Non-Stationary Fuzzy Reasoning in Clinical Decision Support

Jon Garibaldi

Intelligent Modelling and Analysis (IMA) Research Group
School of Computer Science
University of Nottingham, UK

Outline

• Research Motivation
• Definitions
  ‣ type-1 fuzzy sets
  ‣ type-2 fuzzy sets
  ‣ non-stationary fuzzy sets
• Fuzzy Ensemble Reasoning
  ‣ Umbilical Acid-Base Analysis
  ‣ Breast Cancer
• Discussion and future directions

Variability in Decision Making

• Average decisions are not necessarily good
  ‣ car approaches roundabout with three exits
    ‣ driver says “turn left”
    ‣ passenger (navigator) says “turn right”
      1. go left?
      2. go right?
      3. stop and ask for more information?
      4. take the average and go straight-on?!
• Consistent decisions are not necessarily good
  ‣ antelope (prey) evading lion (predator)?
  ‣ limit cycle of robot behaviours

Expert Variation

• Human experts exhibit non-deterministic behaviour in decision making
• For the same inputs, variation may occur
  ‣ among the decisions of a panel of human experts
    ‣ inter-expert variability
  ‣ in the decisions of an individual expert over time or changing circumstances
    ‣ intra-expert variability

Immediate Neonatal Assessment

What has caused the problem?

umbilical cord arteries vein

Difficulties with Assessment

• Need pH and BD_{ecf} from both artery and vein
  ‣ sampling difficult, 25% errors
• Difficult to interpret
  ‣ pH_{A}, BD_{A}, pH_{V}, BD_{V} (4D data)
  ‣ considerable expertise required
• Best if done on every delivery
  ‣ lack of staff availability
Assessing Difficult Cases

- Six experts ranked 50 cases from ‘worst’ to ‘best’ in terms of likelihood of the infant having suffered damage due to oxygen lack
  - an independent expert chose a set of ‘difficult’ cases from a wide range of outcomes
  - cases assessed on the basis of UAB results alone
- Expert system output was arbitrarily scaled
  - absolute comparison to target output was difficult
  - Spearman ranking order correlation

Observed Variation in Opinions

Research Motivation

- To create ‘truly’ intelligent systems that cannot be differentiated from their human counterparts
  - in order to pass a mini-Turing test for evaluation
- To produce a span of decisions that may be arrived at by a panel of experts
  - implement ensemble decision making
- To investigate meaningful decision boundaries

Crisp Sets

Crisp Sets?

Prime Numbers

Numbers less than 20

Numbers less than 20
**Fuzzy Sets**

Formal Definition

- A fuzzy set, $A$, of a universe of discourse $X$ is characterised by a membership function $\mu_A : X \rightarrow [0,1]$ which associates with each element $x$ of $X$ a number $\mu_A(x)$ in the unit interval $[0,1]$.
  - first proposed by Zadeh, 1965
  - formalised by Zadeh, 1975

**Linguistic Variables**

Aside 1: Fuzzy v. Probability

- The notion of membership in fuzzy sets is most closely associated with the notion of 'compatibility'
  - this is not the same as probability
- Consider two bottles containing liquid
  - A has probability 0.9 that it is 'drinkable'
  - B has membership 0.9 in the fuzzy set 'drinkable'
  - which do you drink?

**However ...**

Type-2 Fuzzy Sets

- A height of 1.8m now has a membership of the type-2 fuzzy set tall of between 0.87 and 0.93
  - While there is now a 'blurring' of the membership, there is still no variability.
The membership function wobbles from side to side (for example), so that each time we get a different $\mu$.

Formal Definition

- Let $A$ be a fuzzy set and $T$ a set of time points.
- A non-stationary fuzzy set, $\hat{A}$, of a universe of discourse $X$ is characterised by a non-stationary membership function $\mu_A : X \times T \rightarrow [0,1]$ which associates with each element $x$ of $X$ and $t$ of $T$ a time-specific variation of $\mu_A(x)$.
- proposed by Garibaldi, 2005

Perturbation Functions

- Firstly, parameterise the membership function
- then, perturb one (or more) of the parameters $p_i(t) = p_i + k_i f_i(t)$

Type-1 Fuzzy Inference Systems

Type-2 Fuzzy Inference Systems

NS Fuzzy Inference Systems
Ensemble Fuzzy Inference Systems

- Crisp inputs: $x$, $y$
  - Crisp outputs: $y_1 = f(x, t=1)$
  - Crisp outputs: $y_2 = f(x, t=2)$
  - Crisp outputs: $y_n = f(x, t=n)$

- Aggregation: $y_{\text{ensemble}}$

Fuzzy Expert System

- The UAB fuzzy system output is interpreted as:
  - Possibility that infant is damaged from lack of oxygen
  - PIAD: Possibility of Intrapartum Asphyxial Damage

Aside 2: Possibility v. Probability

- Probability ($P$) is associated with likelihood, frequency or proportion
- Possibility ($\pi$) relates to feasibility, ease of attainment or compatibility
- Events may have same possibility & probability
  - $\pi$(coin is heads) $\approx 0.50$
  - $P$(coin is heads) $\approx 0.50$
- But possibility can be greater than probability
  - $\pi$(Jon undresses now) $\approx 1.00$
  - $P$(Jon undresses now) $\approx 0.00$ !!!

Uncertainty in Input Data

- Plateaux represents unknown parameter
- Width of set represents uncertainty in parameter

Type-1 Fuzzy Agreement

- Agreement with clinicians
  - clinicians $\leftrightarrow$ clinicians $\approx 0.91$ (64 rules)
  - crisp $\leftrightarrow$ clinicians $\approx 0.80$ (64 rules)
  - fuzzy $\leftrightarrow$ clinicians $\approx 0.94$ (25 rules)

- Agreement with outcome (Apgar 5, Apgar 1)
  - clinicians $\leftrightarrow$ outcome $\approx 0.64$
  - crisp $\leftrightarrow$ outcome $\approx 0.52$
  - fuzzy $\leftrightarrow$ outcome $\approx 0.65$

Methodology

<table>
<thead>
<tr>
<th>ID</th>
<th>pHa</th>
<th>BDa</th>
<th>pHv</th>
<th>BDv</th>
<th>PIAD Rank</th>
<th>PIAD lower</th>
<th>PIAD upper</th>
<th>PIAD Rank lower</th>
<th>PIAD Rank upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.60</td>
<td>25.0</td>
<td>6.72</td>
<td>22.3</td>
<td>0.99</td>
<td>1</td>
<td>0.75</td>
<td>1.00</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>7.02</td>
<td>12.0</td>
<td>7.08</td>
<td>11.5</td>
<td>0.56</td>
<td>2</td>
<td>0.40</td>
<td>0.80</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>7.27</td>
<td>4.0</td>
<td>7.35</td>
<td>2.0</td>
<td>0.00</td>
<td>3</td>
<td>0.00</td>
<td>0.40</td>
<td>2</td>
</tr>
</tbody>
</table>
Centre Variation

0.01 0 2 0 3 0 4 0 5 0

Type-1 FLS's Rankings

Type-2 FLS's Rankings

0

10

20

30

40

50

0 0 2 0 3 0 4 0 5 0

Width Variation

0.01 0 2 0 3 0 4 0 5 0

Type-1 FLS's Rankings

Type-2 FLS's Rankings

0

10

20

30

40

50

0 0 2 0 3 0 4 0 5 0

Noise Variation

0.01 0 2 0 3 0 4 0 5 0

Type-1 FLS's Rankings

Type-2 FLS's Rankings

0

10

20

30

40

50

0 0 2 0 3 0 4 0 5 0

Best Inter-Expert Match

UAB: Summary of Results

• Non-stationary systems with either
  - width or noise variation of 3%
  showed best match with inter- and intra-expert variability (in this application)
• The characteristics of the variation observed for these non-stationary systems closely matched the human variability
Breast Cancer - A Complex Disease

- Breast cancer is 2nd most common in women
  - In 2004, caused 519,000 deaths worldwide
  - 7% of cancer deaths; almost 1% of all deaths

Breast Cancer

- Luminal
- Basal
- HER2

Luminal A
Luminal B

Nottingham Data

- A large database of patients with breast cancer collected over the last twenty years
  - over 2000 patients
  - clinical data (age, tumour size, stage, ...)
  - follow-up information (survival, recurrence, ...)
  - tissue samples (including frozen)
    - allows modern bioinformatic analysis on past cases
  - protein expression levels on many biomarkers
- A set of 1076 patients x 25 protein markers

Six Core Classes

Selection of Adjuvant Therapy

- Breast cancer post operative (adjuvant) treatment decision data
- From City Hospital Nottingham Breast Institute (multidisciplinary team)
- Treatment Decisions
  - hormone therapy
  - radiotherapy
  - chemotherapy
  - further operation
  - follow up

Novel Sub-Types Discovered

- ER+
- CKs+
- HER2+
- ER-
- CKs-
- Mixed Class (7.1%)
**Adjuvant Therapy Guidelines**

<table>
<thead>
<tr>
<th>NPI</th>
<th>ER</th>
<th>NSFI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.0</td>
<td></td>
<td></td>
<td>No Adjunct Treatment</td>
</tr>
<tr>
<td>3.1 – 4.4</td>
<td></td>
<td></td>
<td>Recommend Hormone therapy</td>
</tr>
<tr>
<td>&gt; 4.4</td>
<td></td>
<td></td>
<td>Recommend Chemotherapy if VI</td>
</tr>
</tbody>
</table>

**Fuzzy Rules for Chemotherapy**

<table>
<thead>
<tr>
<th>Rule Antecedent</th>
<th>Correspondent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF (NPI is Low)</td>
<td>THEN (Chem to No)</td>
</tr>
<tr>
<td>IF (NPI is Medium) and (ER is not Negative)</td>
<td>THEN (Chem to No)</td>
</tr>
<tr>
<td>IF (NPI is Medium) and (ER is Negative)</td>
<td>THEN (Chem to Maybe)</td>
</tr>
<tr>
<td>IF (NPI is Low) and (ER is Low)</td>
<td>THEN (Chem to No)</td>
</tr>
<tr>
<td>IF (NPI is Low) and (ER is High)</td>
<td>THEN (Chem to Maybe)</td>
</tr>
<tr>
<td>IF (NPI is Low) and (ER is High) and (Age is Young)</td>
<td>THEN (Chem to No)</td>
</tr>
<tr>
<td>IF (NPI is Low) and (ER is High) and (Age is Old)</td>
<td>THEN (Chem to Maybe)</td>
</tr>
<tr>
<td>IF (NPI is Low) and (ER is High) and (ULH is Negative)</td>
<td>THEN (Chem to No)</td>
</tr>
</tbody>
</table>

**NSFIS Ensemble Improves Agreement**

- **NSFIS Ensemble Agreement**
  - Best Non-Stationary Ensemble Agreement: 1141 (87.4%)
  - Original Fuzzy Agreement: 1108 (84.8%)

**Discussion & Future Directions**

- Fuzzy sets and reasoning allows the representation and manipulation of various forms of uncertainty
  - model uncertainty in both data and knowledge
  - demonstrable benefits over non-fuzzy inference
  - non-stationary fuzzy sets model human variability
  - fuzzy ensembles improve performance
- Further theoretical developments required
  - complete framework of fuzzy ensemble reasoning
  - determination/interpretation of non-stationary sets
  - empirical studies of fuzzy ensemble reasoning

**Acknowledgements**

- An Investigation into Non-Deterministic Fuzzy Reasoning (GR/R55085/01)
- Towards a Framework for Modelling Variation in Automated Decision Support (EP/C542207/1)
- BIOPTRAIN: Bioinformatics Optimisation Training (FP6 MC-EST-2007-007397)
- Daniele Soria, Khairul Rasmani
  - (KAR was supported by the Malaysian Government)
- Ian Ellis, Andy Green, Des Powe, Graham Ball
  - all members of the Nottingham Breast Cancer Pathology RG
- Elia Biganzoli, Paulo Lisboa
- Bob John, Shang-Ming Zhou, Xiao-Ying Wang

Thank You!