Prediction of Bladder Cancer Recurrences using Artificial Neural Networks

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Agenda

1.-Introduction

2.-Problem: Cancer prediction

3.-Methodology

4.-Results

5.-Conclusions

Introduction I

- Bladder cancer remains a highly prevalent and lethal malignancy.
  - Transitional Cell Carcinoma or TCC
- Bladder cancer is a very common cancer
  - with 357,000 new cases each year
  - 145,000 deaths each year worldwide
  - and 107,400 new cases in Europe in 2006

Introduction II

- Urine cytology detects tumour cells in urine:
  - Cheap and not invasive
  - Low sensibility (66%-79%) for low grade tumors (too many false positives)
- Cystoscopy, direct observation of the bladder:
  - Relatively sensitive and specific
  - Expensive, invasive and uncomfortable

Introduction III

- Biomarkers:
  - There are some urine-based test but are not better than cystoscopy.
- due the lack of current clinical methods to predict disease recurrence, we have proposed the following solution
  - The integration of classical and non-invasive urine parameters using ANN

Problem of Cancer prediction I

- There is no good solution for clinical monitorisation of bladder cancer patients:
  - Simple
  - Cheap
  - Non-invasive.

- Bladder cancer recurrences or the reappearance of the tumour after its surgical resection cannot be predicted in the current clinical setting

Problem of Cancer prediction II

- We have applied Artificial Neural Networks (ANN) to predict post surgical recurrences in bladder cancer patients.
  - Classical clinical parameters (stage-grade and age)
    - Stage: Superficial (Ta, TIS or T1) or invasive (T2,T3,T4)
    - Grade: Decreasing differentiation degree of tumour cells (G1,G2,G3)
  - 2 urinary markers (growth factor and pro-inflammatory mediator)
  - We have tried different ANN architectures and different training choices.

Methodology I

- Data set:
  - We have 145 patients diagnosed of TCC
    - Stage, Grade and Age
  - We have 118 patients from the set before with urine levels of GF and PF before resection (GF1 and PF1)
  - We 63 patients from the set before with urine measurements 6 moths after surgery (GF2 and PF2)

Methodology II

- Input parameters in disease prediction:
  - Classical input parameters:
    - Stage, Grade and Age
  - Proposed biomarker:
    - Urine levels of GF and PF before resection
    - Urine levels of GF and PF 6 moths after surgery

Methodology III

- Output parameters in disease prediction:
  - Recurrence1:
    - Tumor presence when the second urine samples is collected
  - Recurrence2:
    - Tumor recurrence in a 2 year follow-up period after the tumor resection.

Methodology IV

- Data set information:

WITH DATA FOR OUTPUT VARIABLE	**Recurrence1** (Recurrent / Non recurrent)	**Recurrence2** (Recurrent / Non recurrent)
TOTAL	5 / 58	40 / 104
WITH INPUT PARAMETER DATA		
Age	5 / 30	28 / 69
Stage-Grade	5 / 58	33 / 46
GF1	5 / 58	31 / 85
PF1	5 / 48	30 / 75
GF2	5 / 57	20 / 33
PF2	5 / 48	23 / 39
WITH COMPLETE DATA	5 / 24	12 / 17

Methodology V

- ANN Architectures:
  - Architecture, MLP-BP:
    - We have tried different input sets

	NEURONS IN INPUT LAYER	INPUT PARAMETERS	HIDDEN LAYERS	HIDDEN LAYER NEURONS	OUTPUT LAYERS:VARIABLE
MLP21/MLPA	4	PF1, GF1, PF2, GF2	1	4	1: Recurrence1 / Recurrence2
MLP22/MLPB	5	PF1, GF1, PF2, GF2, AGE		5	
MLP23/MLPC	5	PF1, GF1, PF2, GF2, STAGE-GRADE		5	
MLP24/MLPD	6	PF1, GF1, PF2, GF2, AGE, STAGE-GRADE		6	
MLPE	2	AGE, STAGE-GRADE		2	

Methodology VI

- ANN Training options:
  - Over training of the patterns with positive values for the output variable Recurrence1
    - This aimed to compensate for the low number of cases available for this output variable with early relapse
  - Due to the relatively low number of patients considered in the available dataset a strategy of defining as many networks as patients minus 1 was followed.
    - The network was trained with all patients except for one, which was used as the validation patient, and the correct prediction ratio estimated.

Results I

Total prediction rates of early recurrences (output variable Recurrence1)

TRAINING	TYPE A		TYPE B		TYPE C		TYPE D	
OVER TRAINING	YES		NO		YES		NO	
TRANSFER FUNCTION*	logsig				tagsig			
SOURCE DATA**	**C**	**I**	**C**	**I**	**C**	**I**	**C**	**I**
MLPA (PF1, GF1, PF2, GF2)	**95,23 %**	94,48 %	88,89 %	94,48 %	90,48 %	**95,17 %**	90,48 %	94,48 %
MLPB (PF1, GF1, PF2, GF2, AGE)	92,06 %	94,48 %	87,30 %	93,79 %	88,89 %	92,41 %	88,89 %	93,79 %
MLPC (PF1, GF1, PF2, GF2, STAGE-GRADE)	90,47 %	93,10 %	90,48 %	**95,17 %**	82,54 %	**95,86 %**	87,30 %	**95,17 %**
MLPD (PF1, GF1, PF2, GF2, AGE, STAGE-GRADE)	88,89 %	92,41 %	90,48 %	93,79 %	92,06 %	**95,17 %**	87,30 %	**95,86 %**
MLPE (AGE, STAGE-GRADE)	93,65 %	81,38 %	93,65 %	82,07 %	92,06 %	83,45 %	92,06 %	82,07 %

* Transfer function: logarithmic sigmoid and hyperbolic tangent

** Source data: C) Only patients with complete data considered; I) All available patients considered even if their data was incomplete.

Results II

Total prediction rates of recurrences in 2 years

	FILTER 0	FILTER 1	FILTER 2	FILTER 3	FILTER 4	FILTER 5
Maximum number of unknown parameters	0	1	2	3	4	5
TRAINING	**MLPA** (PF1, GF1, PF2, GF2)					
Type A	72,41 %	79,25 %	79,10 %	71,15 %	72,50 %	60,00 %
Type B	72,41 %	79,25 %	77,61 %	70,19 %	68,33 %	68,28 %
Type C	79,31 %	81,13 %	76,12 %	75,96 %	71,67 %	68,97 %
Type D	72,41 %	77,36 %	77,61 %	69,23 %	68,33 %	70,34 %
TRAINING	**MLPB** (PF1, GF1, PF2, GF2, AGE)					
Type A	72,41 %	83,02 %	71,64 %	77,88 %	74,17 %	64,14 %
Type B	75,86 %	81,13 %	77,61 %	77,88 %	68,33 %	60,69 %
Type C	72,41 %	83,02 %	79,10 %	70,19 %	75,00 %	68,28 %
Type D	75,86 %	77,36 %	76,12 %	70,19 %	74,17 %	64,83 %
TRAINING	**MLPC** (PF1, GF1, PF2, GF2, STAGE-GRADE)					
Type A	72,41 %	**88,68 %**	77,61 %	69,23 %	66,67 %	64,14 %
Type B	68,97 %	**86,79 %**	79,10 %	77,88 %	65,00 %	63,45 %
Type C	82,76 %	83,02 %	80,60 %	78,85 %	68,33 %	64,14 %
Type D	75,86 %	83,02 %	77,61 %	66,35 %	65,00 %	71,03 %

Results III

Total prediction rates of recurrences in 2 years

	FILTER 0	FILTER 1	FILTER 2	FILTER 3	FILTER 4	FILTER 5
Maximum number of unknown parameters	0	1	2	3	4	5
TRAINING	**MLPD** (PF1, GF1, PF2, GF2, AGE, STAGE-GRADE)					
Type A	68,97 %	83,02 %	77,61 %	76,92 %	69,17 %	62,76 %
Type B	65,52 %	77,36 %	76,12 %	69,23 %	63,33 %	61,38 %
Type C	68,97 %	**86,79 %**	76,12 %	75,00 %	78,33 %	66,90 %
Type D	68,97 %	84,91 %	77,61 %	75,96 %	68,33 %	68,97 %
TRAINING	**MLPE** (AGE, STAGE-GRADE)					
Type A	**86,21 %**	**90,57 %**	80,60 %	76,92 %	76,67 %	61,38 %
Type B	82,76 %	**88,68 %**	70,15 %	70,19 %	71,67 %	57,24 %
Type C	**86,21 %**	**86,79 %**	82,09 %	78,85 %	79,17 %	70,34 %
Type D	68,97 %	**88,68 %**	68,66 %	71,15 %	70,00 %	71,03 %

Conclusions I

- In the case of early recurrences, urinary markers give slightly higher prediction rates than classical parameters (95% and 93% for MLPA and MLPE respectively for Recurrence1 prediction).

Conclusions II

- In contrast, when data of recurrences occurring in a 2 year follow-up period MLPE predict 86-90% of the cases correctly, while MLPA (urinary markers) only gives the right answer for 79-81% of the patients
- The combined use of urinary markers and stage-grade information in MLPC increase their prediction rate to 83%
- When sensitivity and specificity are considered separately rather than integrated in the overall prediction rate, urinary markers highlight very valuable information regarding their clinical use.

Conclusions III

- The ANN designed using MLP for four urinary parameters plus stage-grade (MLPC) allowing a maximum of 2 unknown data in the training dataset (Filter 2) provide the chance to predict 50% of the patients that will recur in 2 years.
  - Currently impossible to predict using clinical data such as stage-grade and age, as demonstrated by the low sensitivity of MLPE.

Conclusions IV

- In this study the use of ANNs has shown to be a valuable tool to discriminate which are the parameters that could be used as recurrence prediction biomarkers.
  - Can be measured along time in non-invasive samples such as urine.
- The validation of such prediction models in larger data collections would provide the means of translating multiparametric data integration models into clinical practice with the final aim of reducing patient suffering and sanitary costs.

Thank you for your attention

Any question?