Next Generation of Adaptive Integrated Testing Strategies for Skin Sensitization

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Background

- Roadmap from ITS conceptual to operational framework
  - ITS drivers & expectations
  - Elements of a testing strategy
  - Challenges to accept model based decision making
  - Bayesian networks
- Skin sensitization ITS-2
  - Evolution of input tests
  - Formalization into a Bayesian Network
    - Evidence synthesis mode (qWoE)
    - Guiding testing strategy mode (VOI)
  - efficiency

Jaworska, Aldenberg, Gabbert 2010, Reg Tox Pharm; Jaworska & Hoffmann 2010, Altex; Jaworska et al. Altex 2011 ITS-1; Aldenberg &Jaworska 2010 qWoE

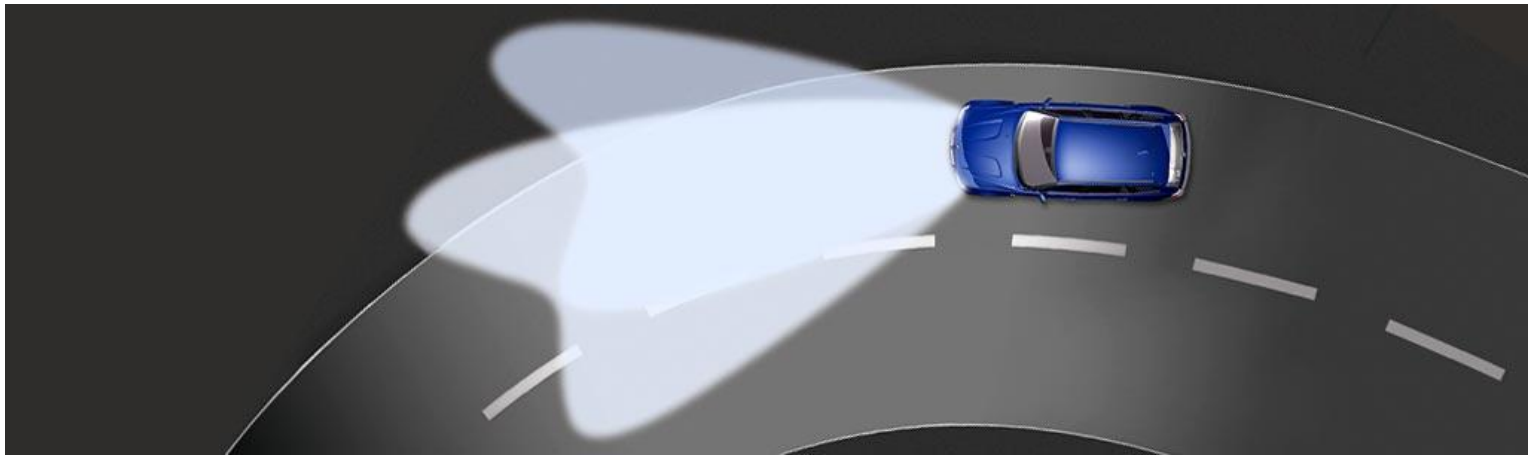
Adaptive and Flexible Testing strategy

A single generic set of tests as a replacement strategy is unlikely to be most effective

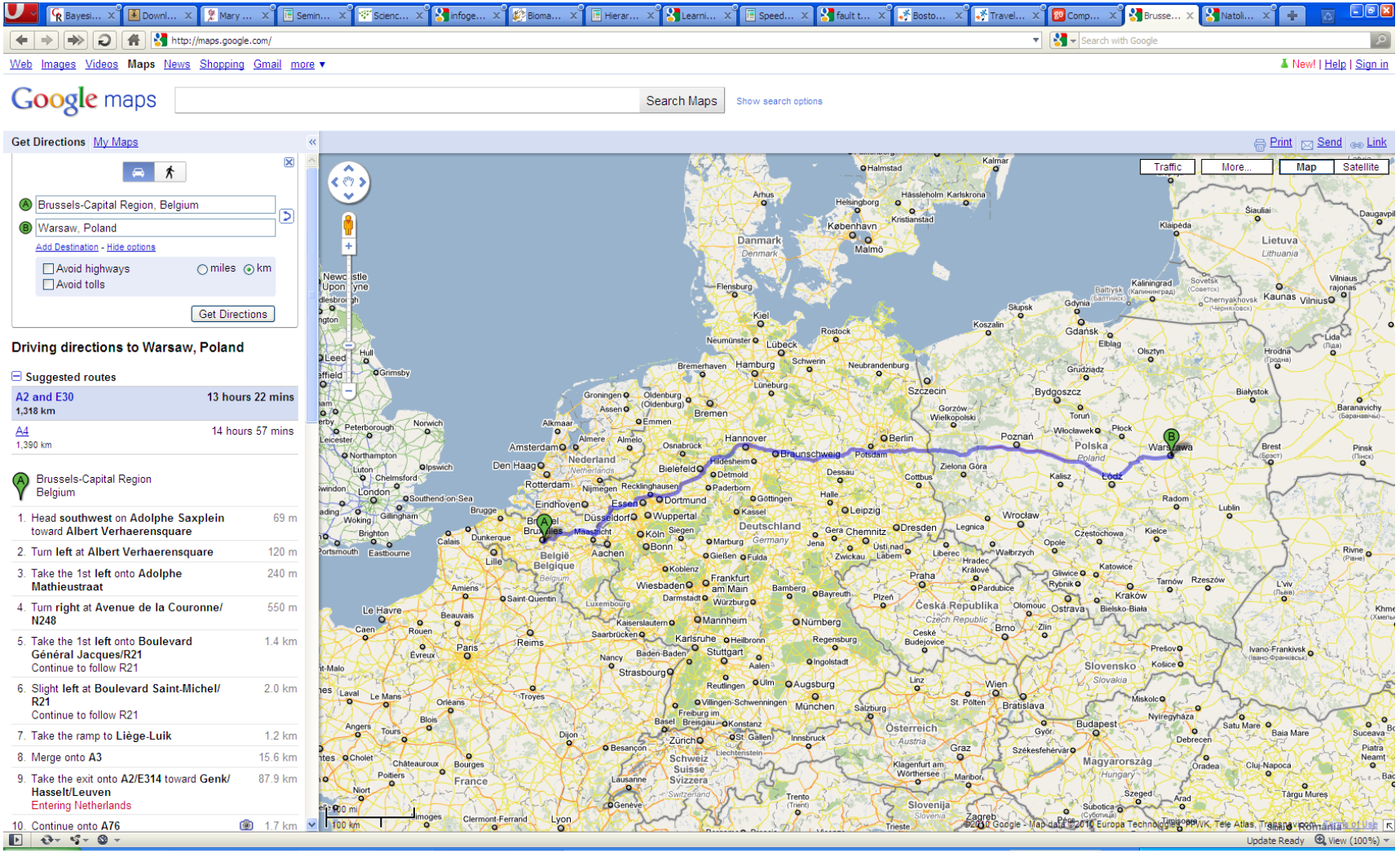
- depends on the initial information
- changes based on additional information

•**Adaptive Headlights in BMW**

Adaptive Headlights ensure that you have the best possible view of the road ahead, even at night. As you enter a curve, the headlight's beam turns to follow the direction of the road. So you always know what's ahead.



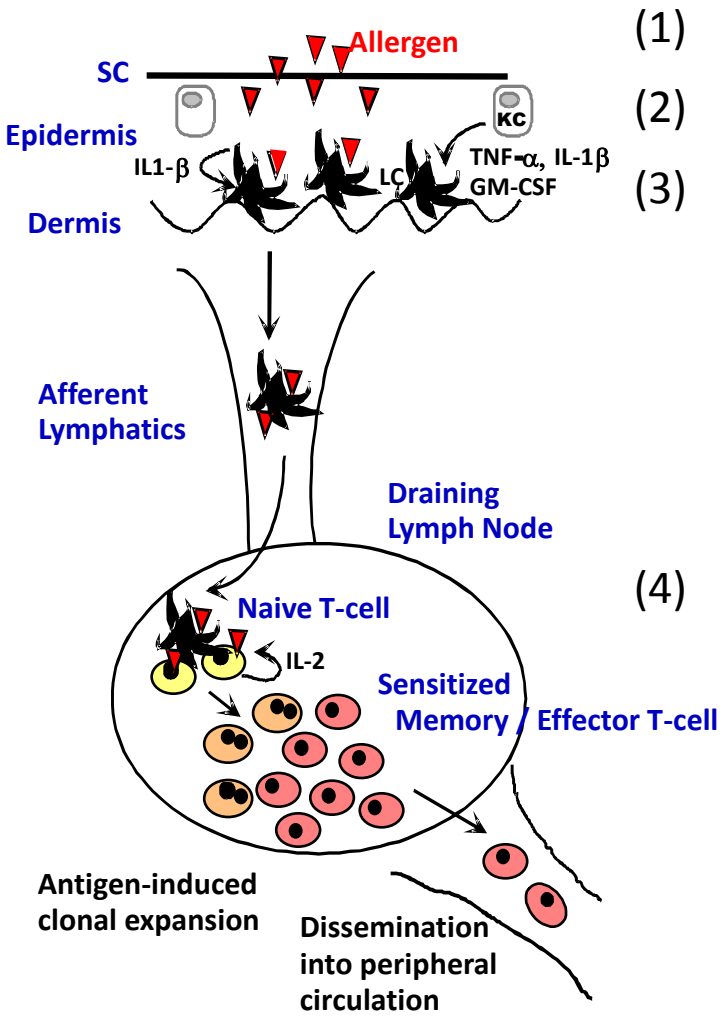
ITS is a toxicological GPS with a dynamic route optimization setting



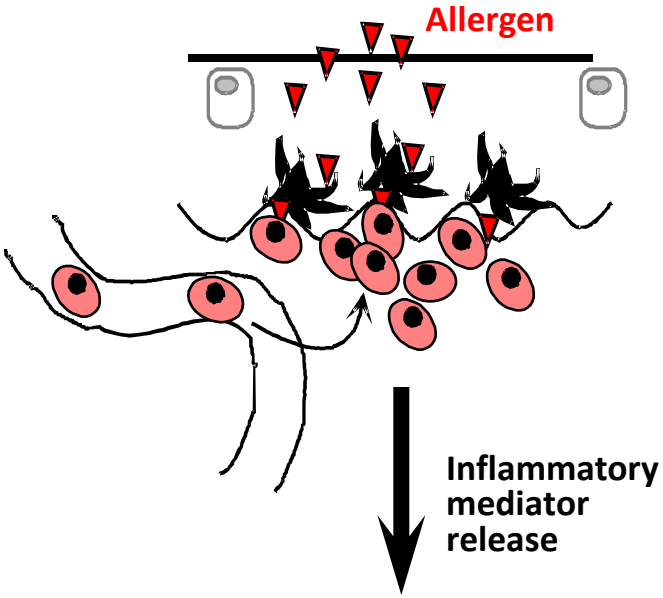
Evidence synthesis vs testing strategy

Skin sensitization mechanism knowledge map

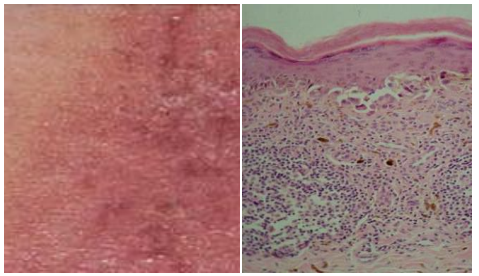
Induction Phase



Elicitation Phase



Erythema
Edema
Vesiculation



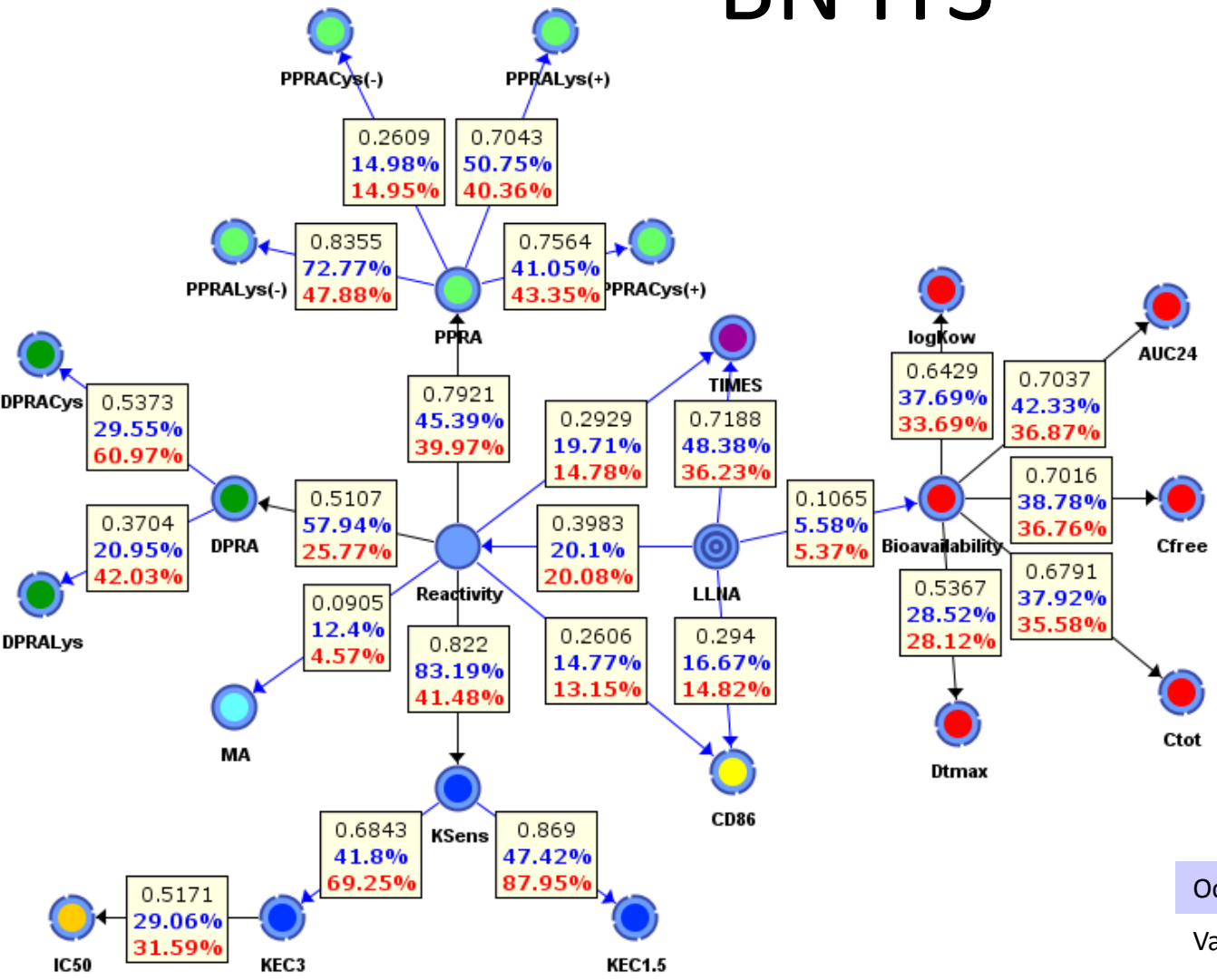
Database

- 137 chemicals with data related to
  - Bioavailability (log Kow, AUC24, Ctot, Cfree)
  - Protein reactivity
    - (DPRA (Cys, Lys); PPRA (Cys (-/+), Lys(+/-); Ksens
  - DC activation (CD86)
  - Overall skin sensitization potential – Times Metabolites,
  - Toxtree Michael Acceptors SMARTS
  - LLNA experimental data NS 29.00% W 22.60% M 28.20% S 20.20%
- 124 training set/13 test set

Process of BN construction

- Follow skin sensitization process
- Combination of knowledge and data
    - Constraints in the form of fixed and forbidden arcs between nodes were specified.
- Conditional dependence characterization by use of latent variables
  - Latent variables are useful way of accumulating dose response information(Ksens) , multiple readouts (PPRA, DPRA), express conceptual quantities

BN ITS



ROC values (%)

LLNA state	Training set	Test set
NS	95	100
W	90	95
M	82	67
S	86	81

Test set predictions

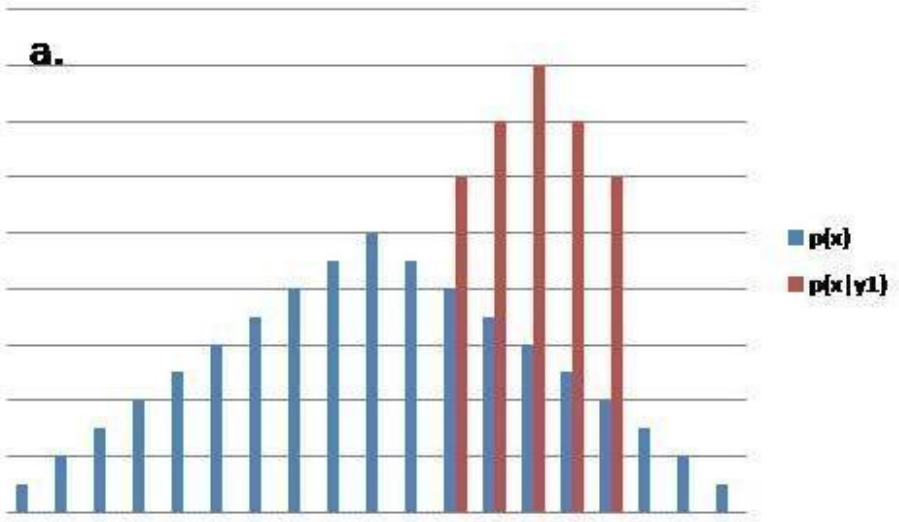
Occurrences				
Value	1 (5)	2 (5)	3 (1)	4 (2)
1 (5)	5	0	0	0
2 (2)	0	4	0	0
3 (5)	0	1	1	1
4 (1)	0	0	0	1

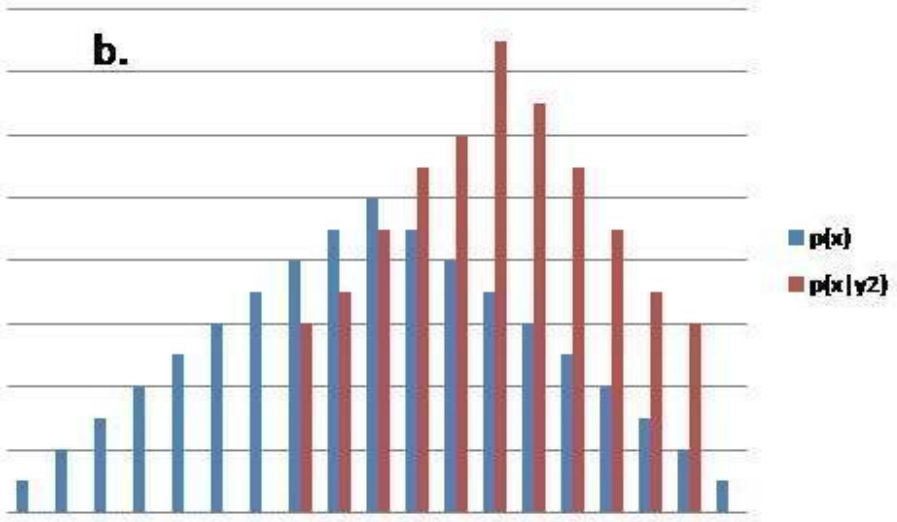
Value of Information (VOI) driven testing strategy

- "**One step look – ahead hypothesis**"
  Amounts to computing the mutual information MI(X, Y) for all possible observations Y and choosing the one that has the highest MI with the hypothesis variable X.

- Mutual Information MI (X, Y)- "the amount of uncertainty in *Y* which is removed by knowing *X*". MI(X, Y) = H(Y)-H(Y|X) .
- Relative MI ,MI(X,Y)/H(Y), yields % of entropy of the parent node Y, H(Y), reduced by knowledge of X

Mutual Information



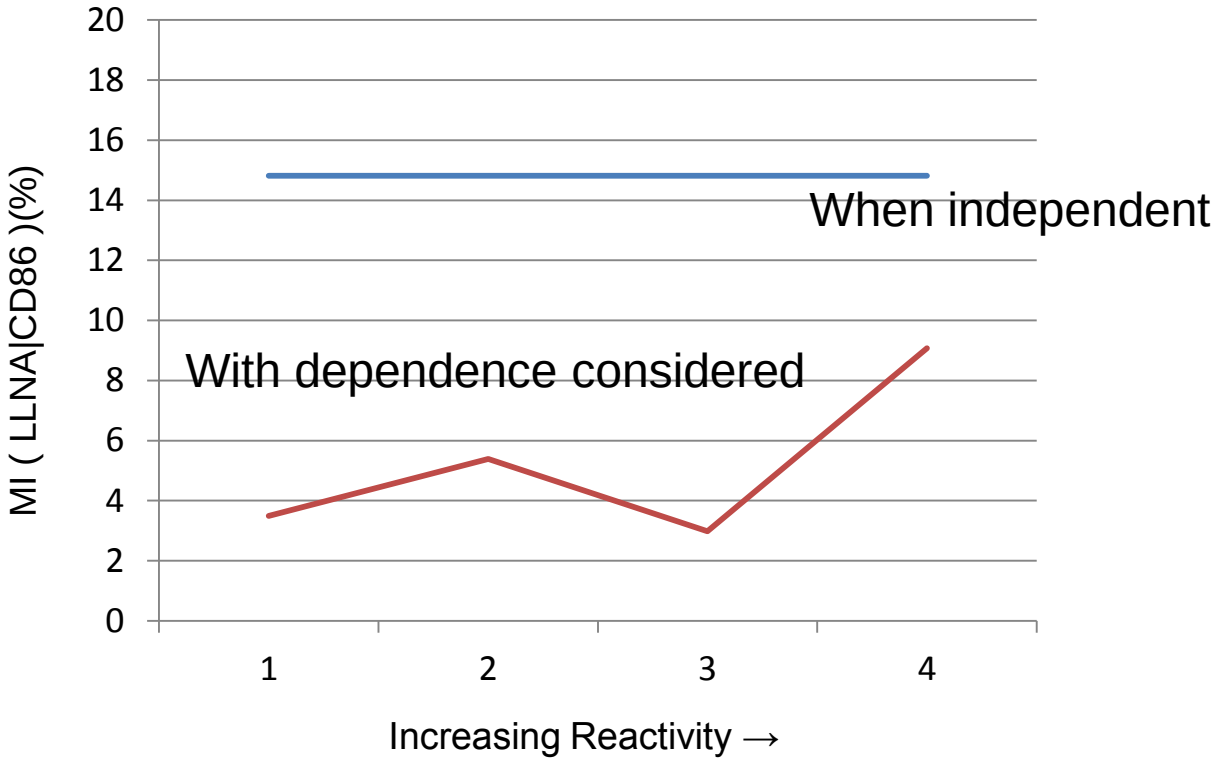


A. y1 shares mutual information with x such that given a y1 the values of x are now narrowed down to the five values.

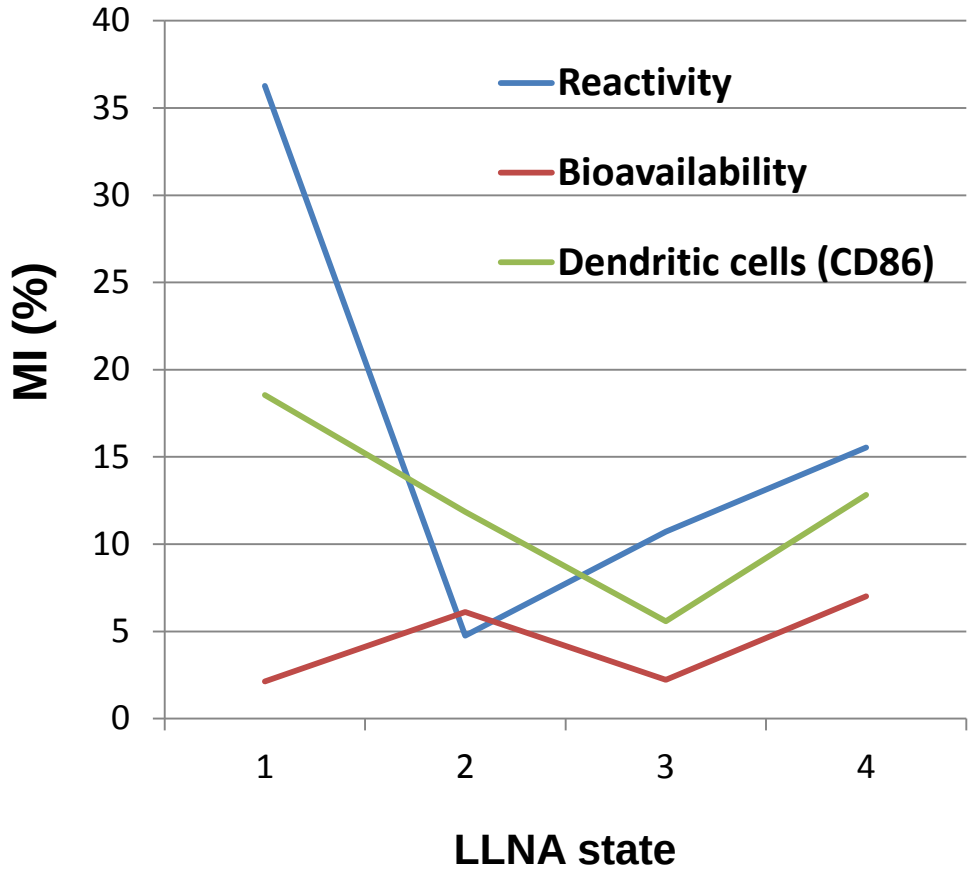
B. y2 shares mutual information with x but it shares less information than y1 and therefore is not as helpful as y1, as it does not eliminate as many potential x values.

Impact analysis on adding DC data info when R is known

- High dependence between CD86 and Reactivity



Ranking of latent variables per LLNA state



•It is easier to identify NS and S, and harder W and M classes. More tests are needed for these classes to achieve similar degree of confidence as for NS and S

Reactivity tests – value of multiple views
Local based MI rankings

- NS: Ksens (26.5%), DPRA (17.5%), PPRA (8%) ; R (36%)
- W: PPRA (0.7%), DPRA (0.4%); Ksens (.3)%, R (5%)
- M: Ksens (8%), DPRA (4.5%), PPRA (1%); R (11%)
- S: PPRA (10%), Ksens (5.5%),DPRA (5.5%); R(15.5%)

Summary

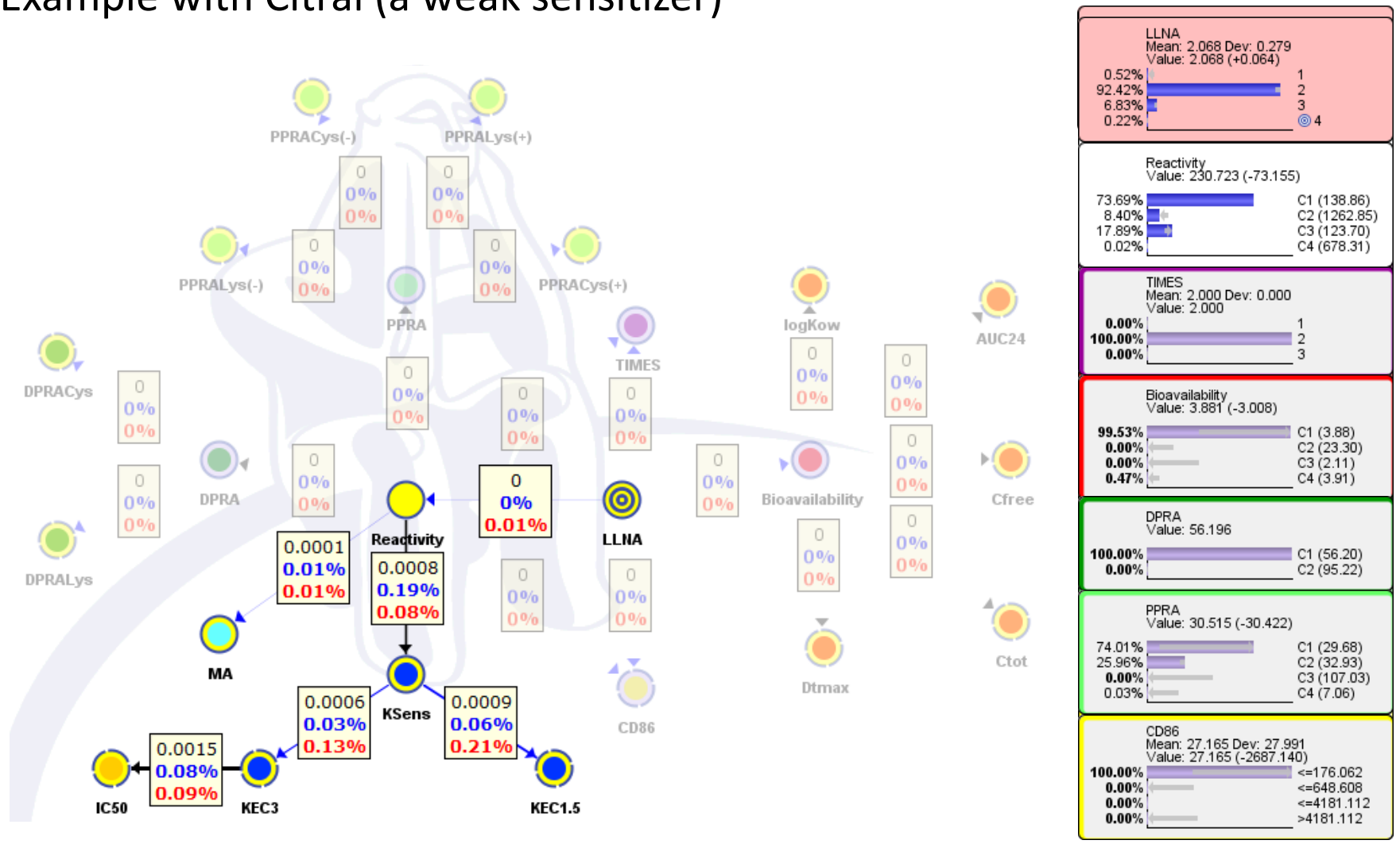
- Times (36%)> Reactivity (20%) > Dendritic cells (15%)> Bioavailability (6%)
- High dependence between CD86 and R, Times and R
- CD86 alone is the most informative individual test 15%* but a combined reactivity is better
- DPRA is slightly more informative than PPRA
  - Cys is more informative than Lys in DPRA
  - Cys+ is more informative than Lys+ in PPRA
- Bioavailability is important for weak sensitizers because reactivity tests are not informative
  - CD86 (11 %)>B(6%)>R(5%)

**The MI numbers are pertinent to this particular network structure and 4-way classification!*

Interactive Inference

CD86 yes R yes TIMES

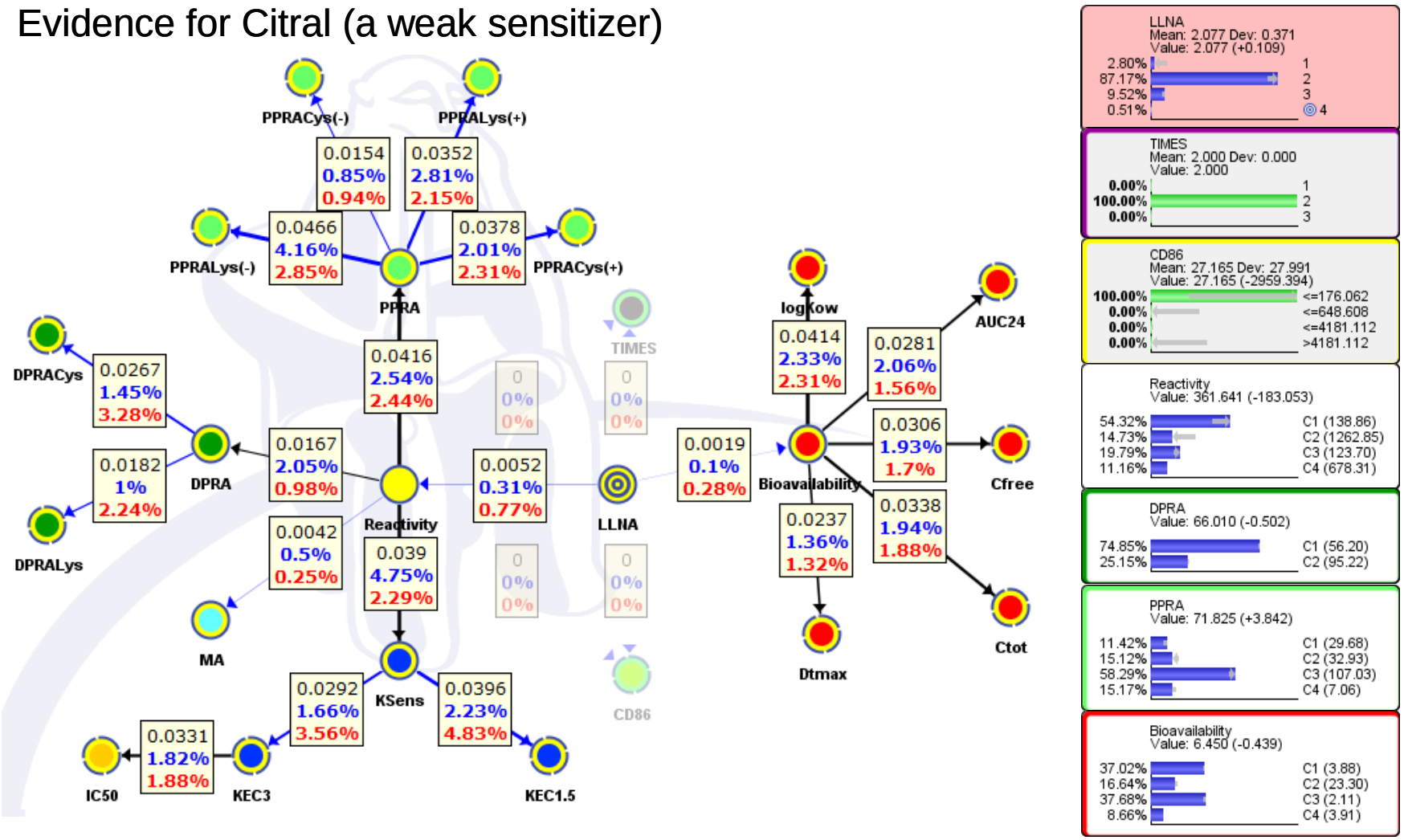
Example with Citral (a weak sensitizer)



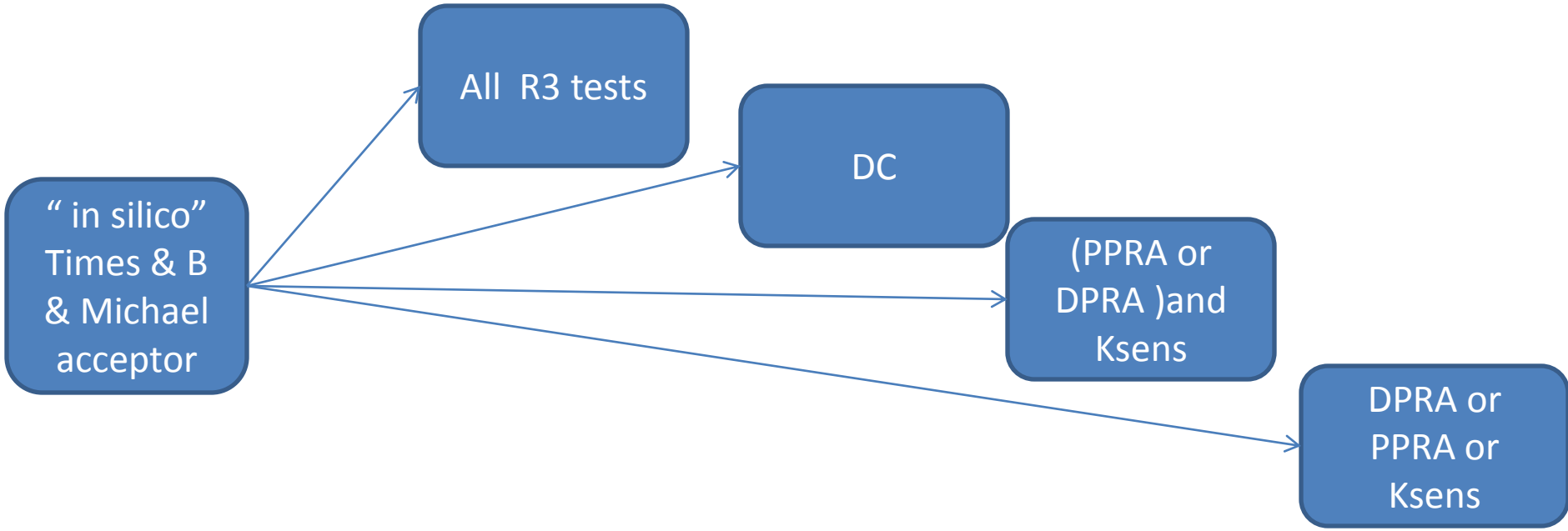
Interactive Inference

CD86 yes R yes TIMES

Evidence for Citral (a weak sensitizer)

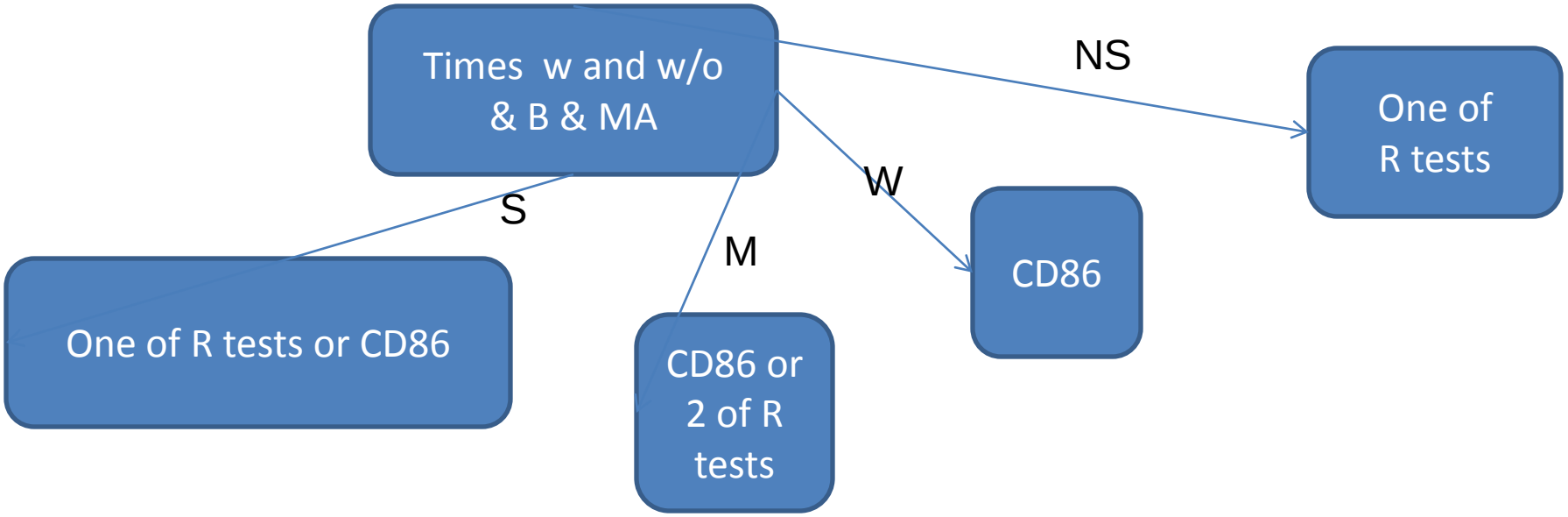


Flexible ITS – there are many ways to get to the final decision



•In silico generated hypothesis is balanced because provides information from 3 different perspectives. Important not to make prior too "heavy". We could add DEREK but it would have to be dependent to Times.

Adaptive ITS



- if in silico data are in agreement (e.g. P(LLNA=x) is >85%, use a in vitro tests for confirmation,
  - Which in vitro test is optimal depends on the hypothesis of LLNA potency, best is to use the test with highest MI
- If Times is not used 2 in vitro tests are needed, most "orthogonal" test are optimal and we can identify them by evaluating Mis.

Final thoughts

- While at this point we focus on scientific credibility of ITS, there are efforts needed to make this type of systematic approach more accessible, viable and practically feasible.

- We can also analyse case studies like this one and ask themselves what if we could do it in freeware?
  - BNs with a functionality of constructing latent variables to capture conditional dependence