

Modulation of QSAR sensitivity / specificity

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Case study:

Aromatic amines

Mutagenic activity in *Salmonella typhimurium* TA100 (+ S9)

QSARs of Aromatic amines: mutagenic activity

Mutagenic activity in *Salmonella typhimurium* TA100 (+ S9)

$$w = \overset{\text{Electronic}}{\downarrow} -2.85 \text{ HOMO} + 1.84 \text{ LUMO} + \overset{\text{Steric}}{\downarrow} 0.70 \text{ MR}_2 + 0.69 \text{ MR}_3 + 1.90 \text{ MR}_6 + 3.36 \text{ Idist}$$

w(mean,Class1) = 26.09 N1 = 47 (non-mutagens)

w(mean,Class2) = 23.99 N2 = 64 (mutagens)

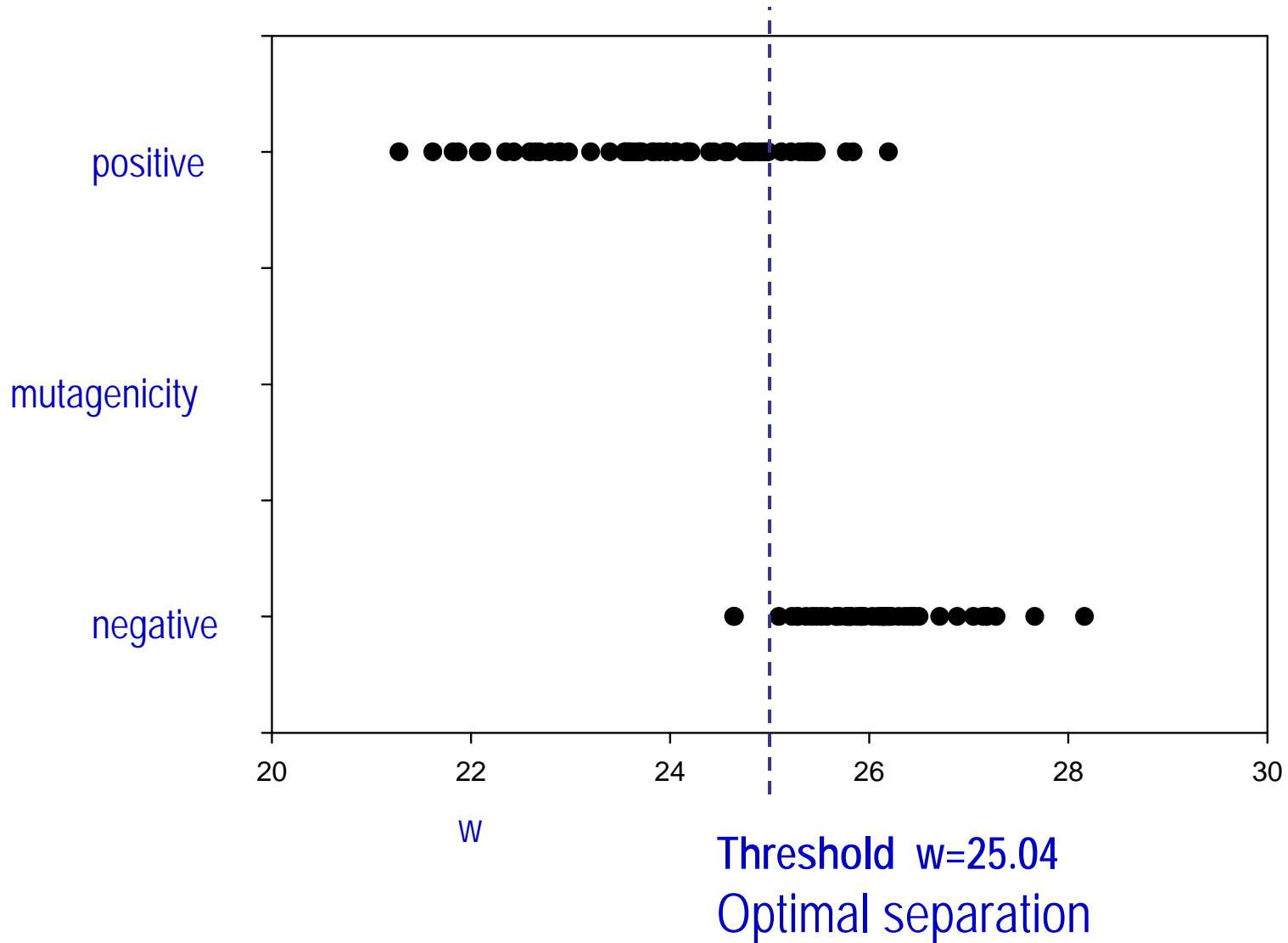
Threshold = 25.04

Canonical Discriminant Analysis, Raw Coefficients

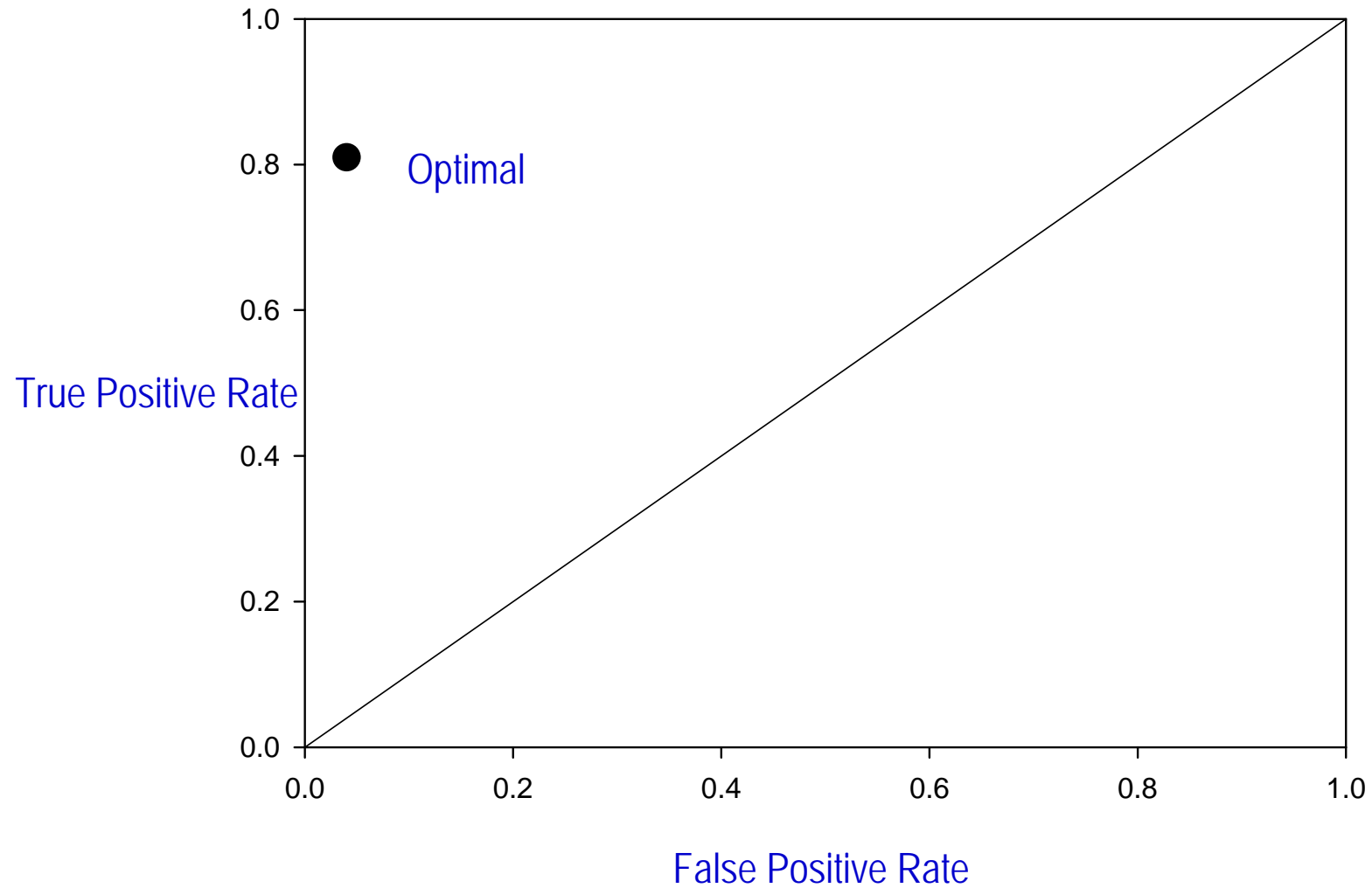
n = 111 (- = 47; + = 64) Correct Classification = 87. %

Benigni et al., 2007

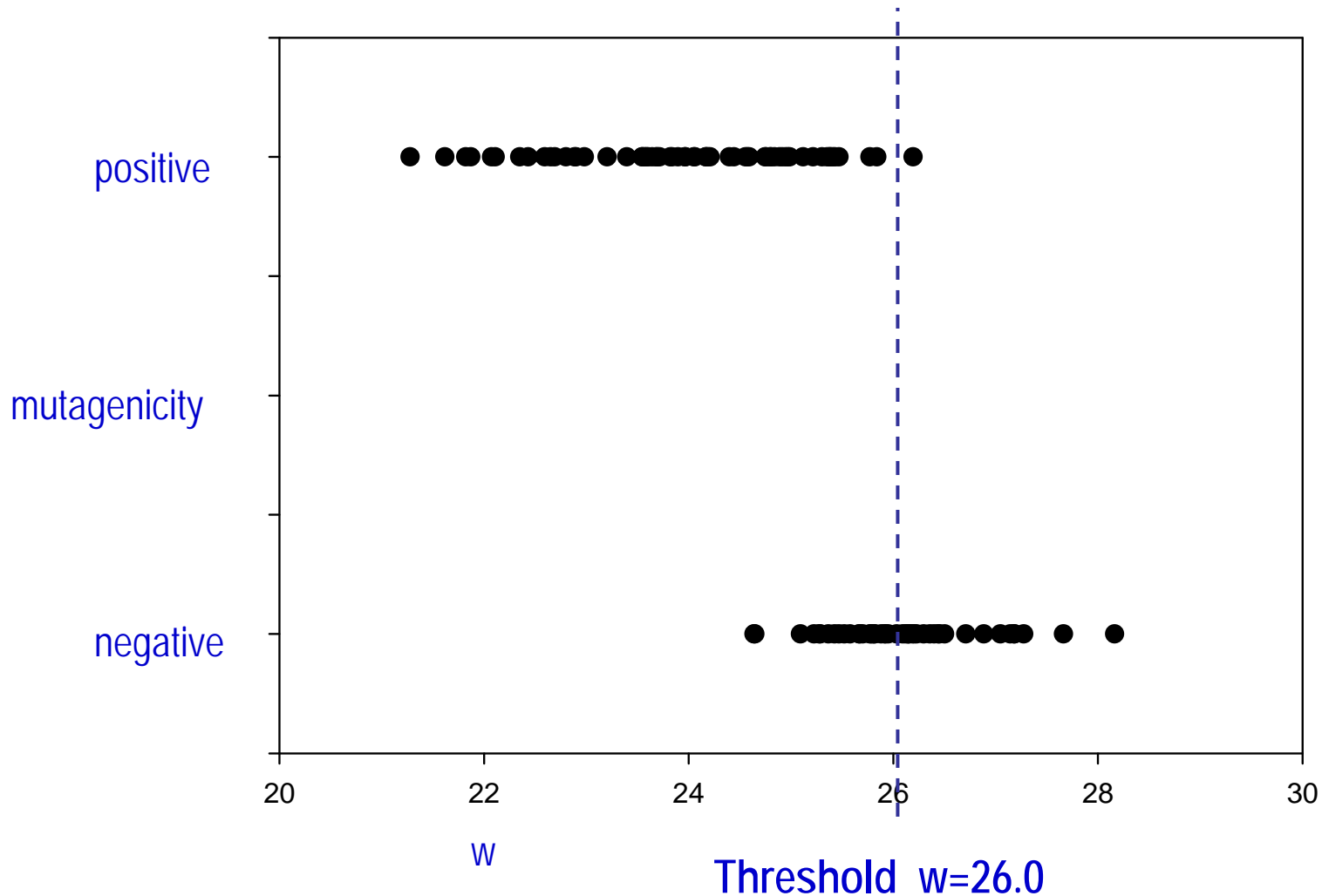
TA100 mutagenicity Training set (n=111)



TA100 mutagenicity Training set (n=111)

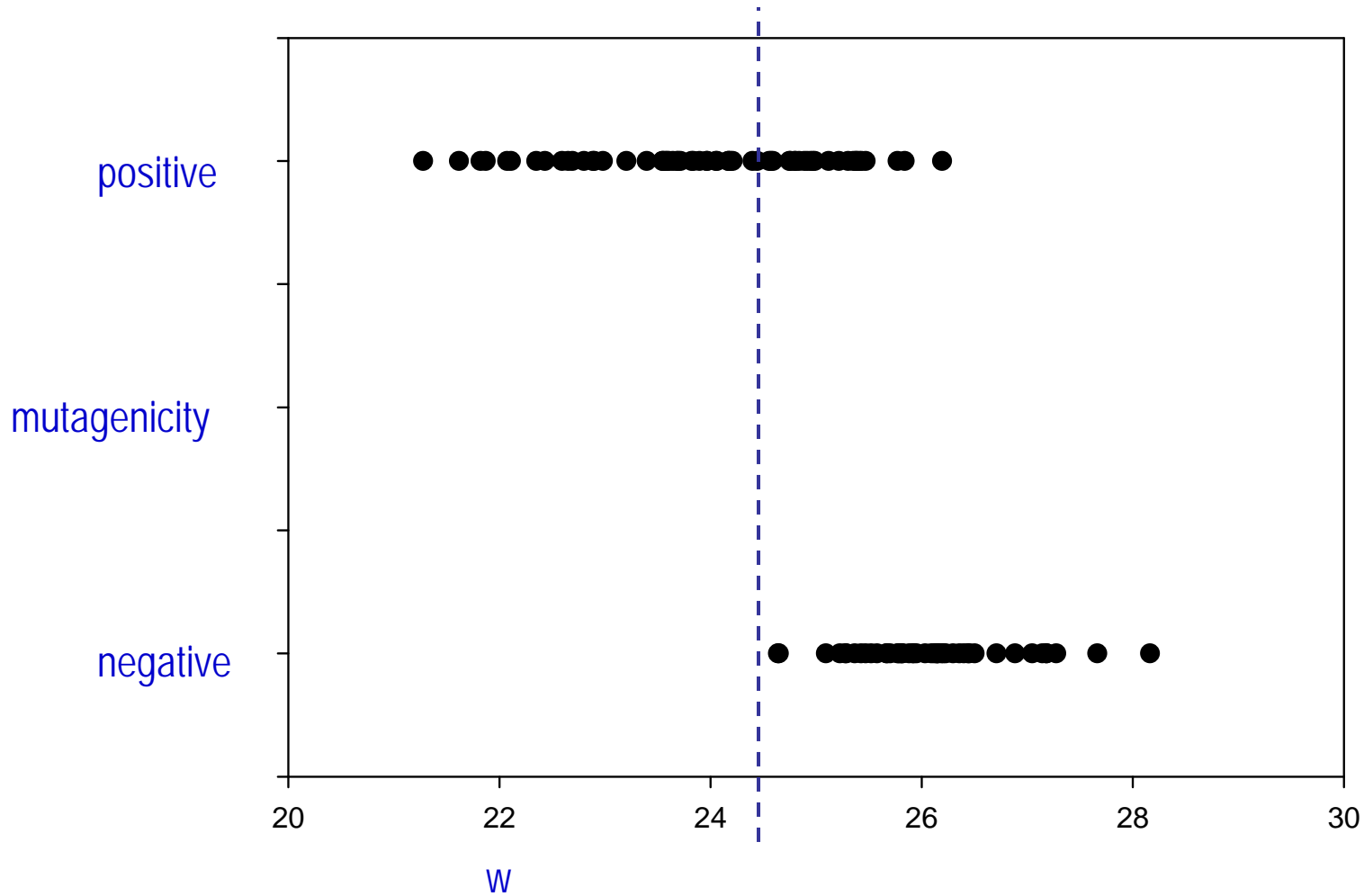


TA100 mutagenicity Training set (n=111)



High sensitivity: reliable prediction of negatives (e.g., safe chemicals)

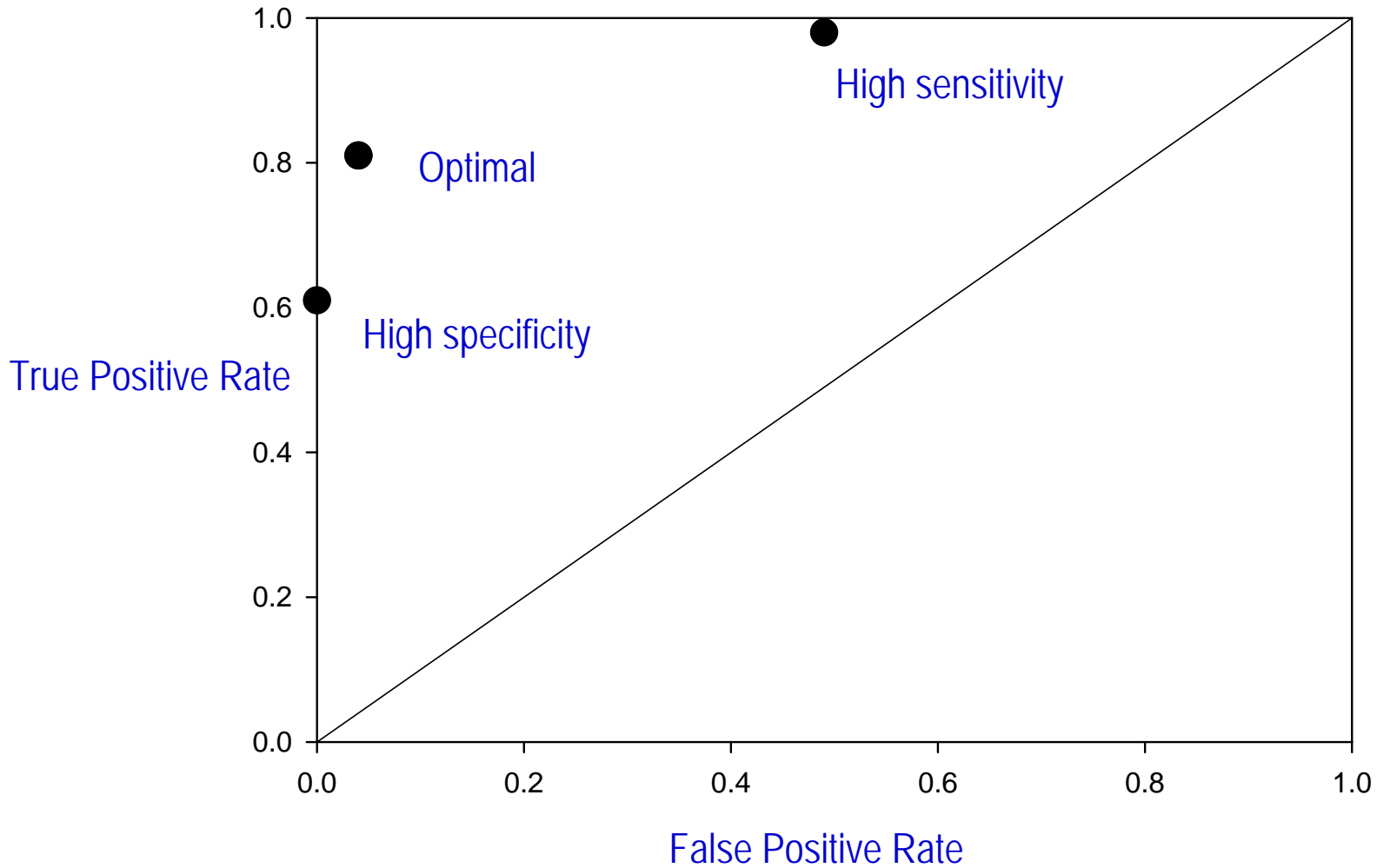
TA100 mutagenicity Training set (n=111)



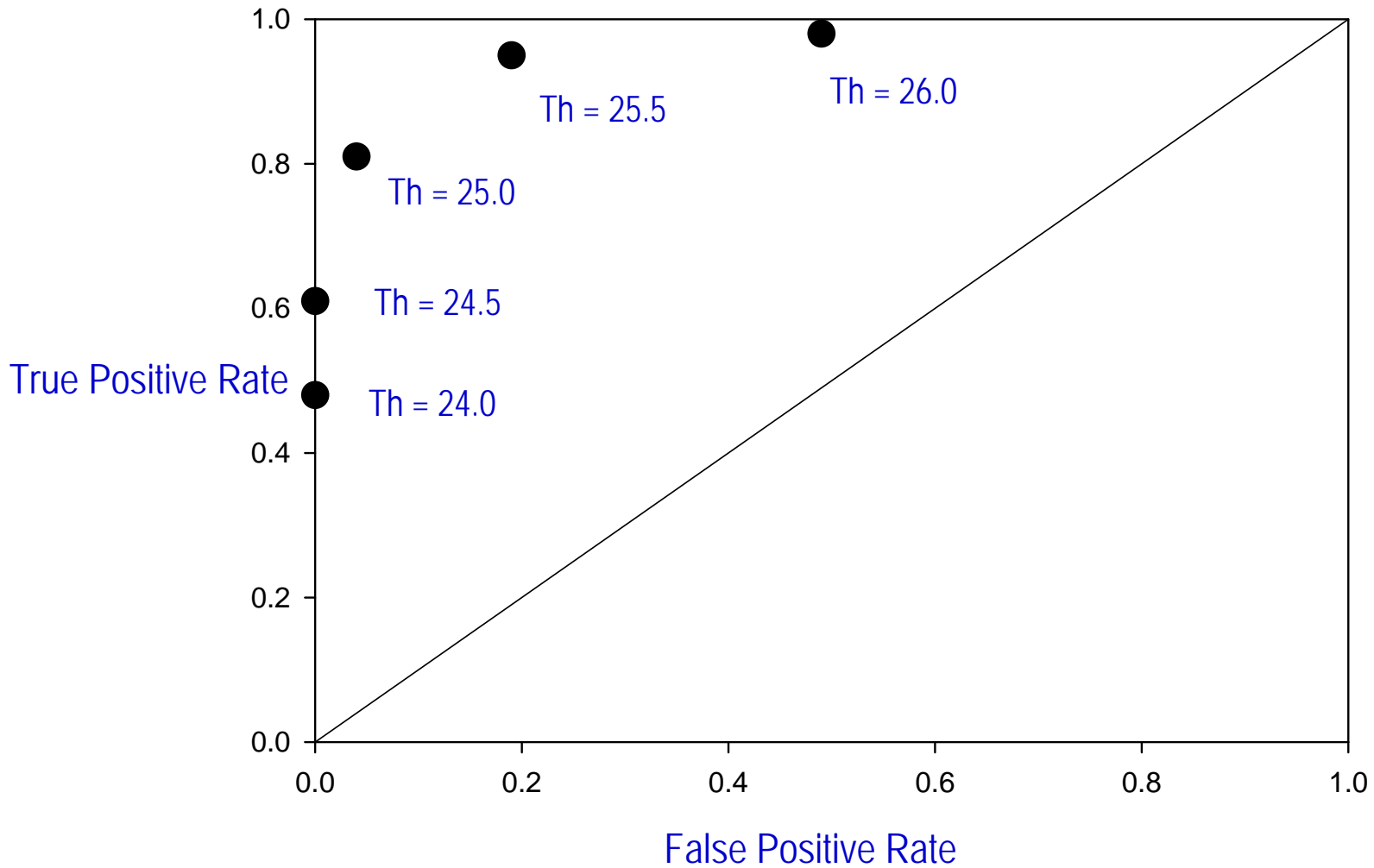
Threshold $w=24.5$

High specificity: positives to be discarded, or actives to be developed

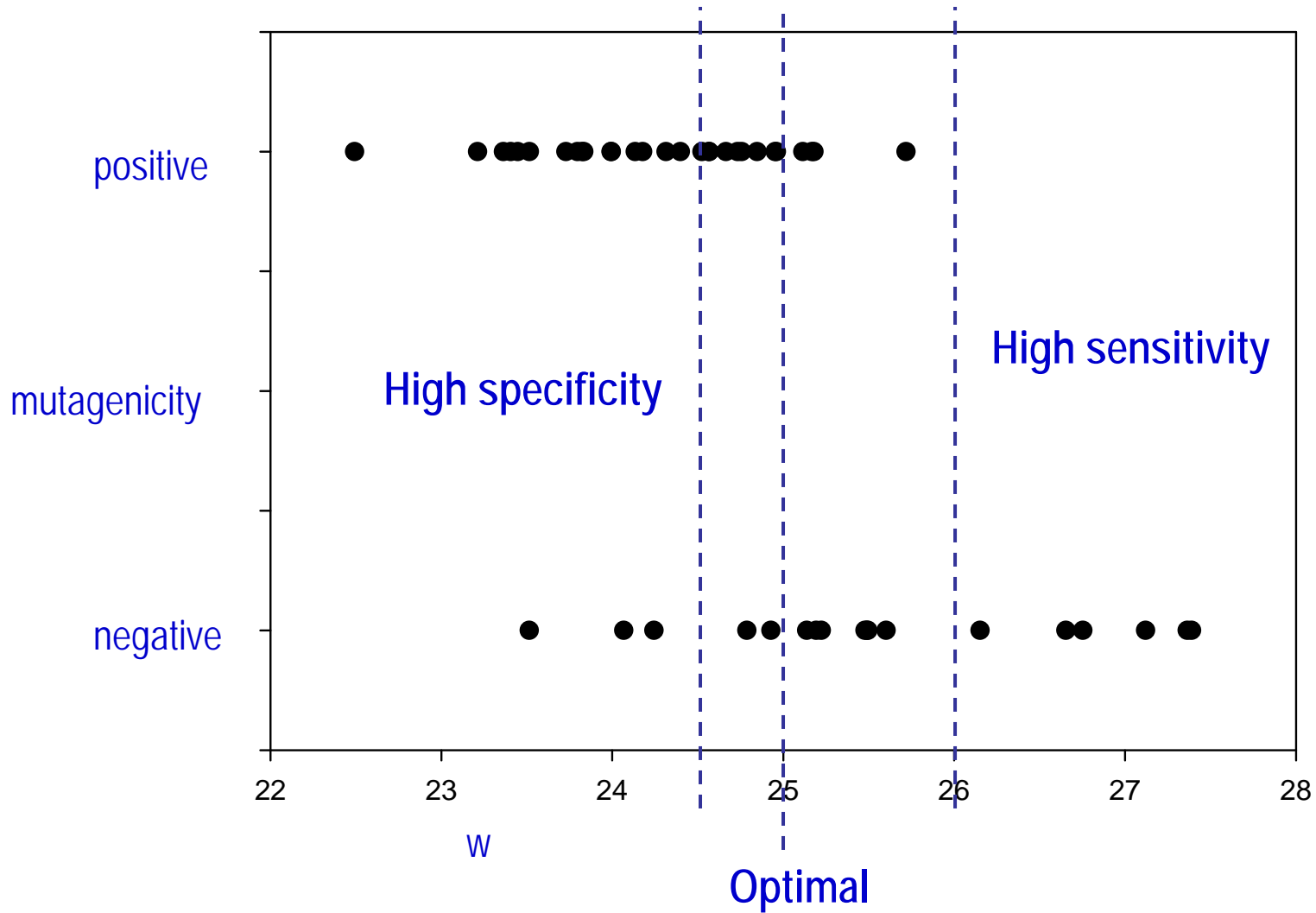
TA100 mutagenicity Training set (n=111)



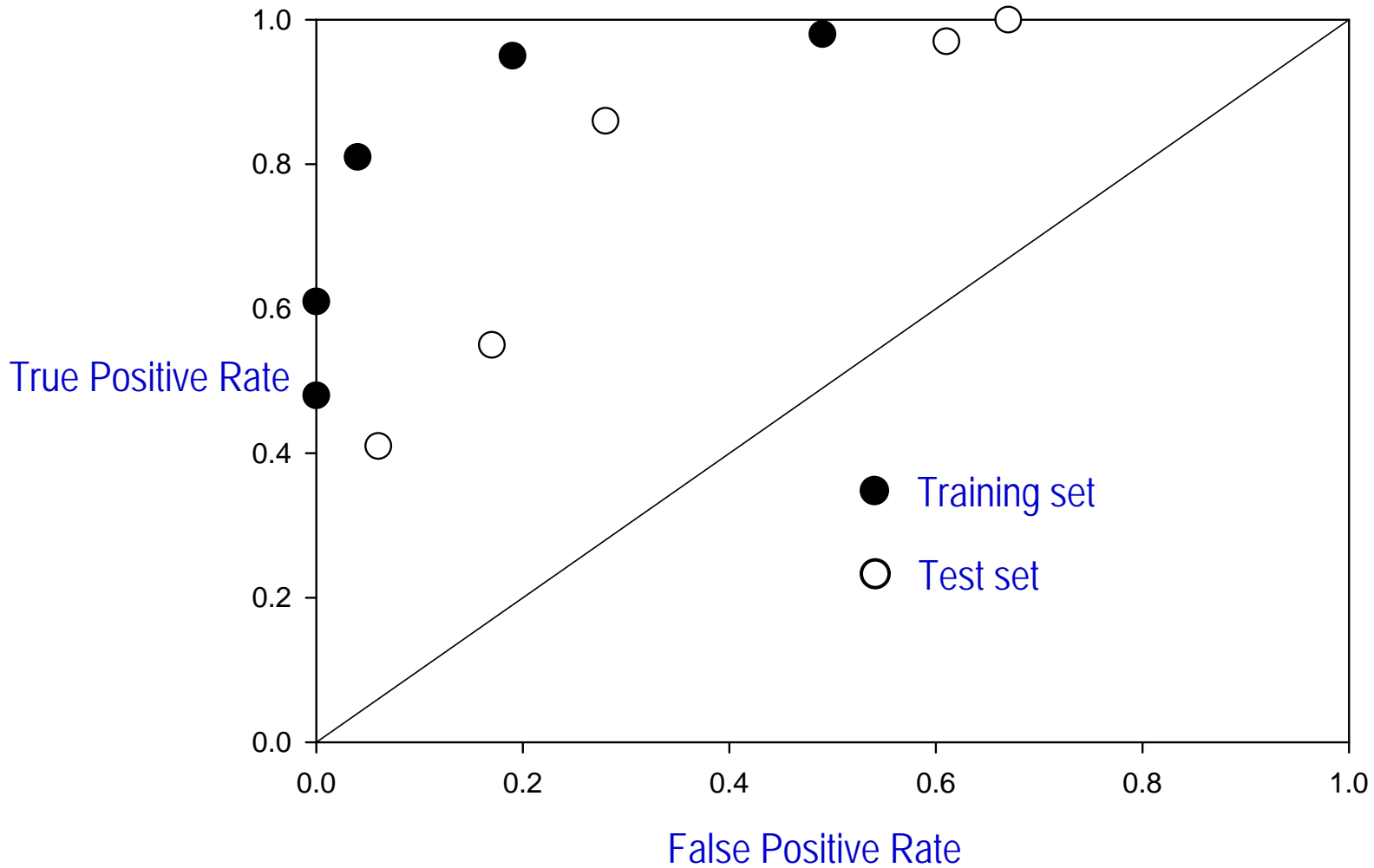
TA100 mutagenicity Training set (n=111)



TA100 mutagenicity Test set (n=47)



TA100 mutagenicity Training and test sets



Conclusions

- Sensitivity / specificity of discriminant QSAR can be custom-tailored

- High sensitivity

Does not miss positives (at the expense of false positives)

High reliability for negatives (e.g., **safe chemicals to be developed**)

- High specificity

Produces false negatives

High reliability for positives (e.g., **toxic chemicals to be discarded;**
promising drugs or perfumes to be developed)

- **More than one option applicable** (ranks of interest)

TA100 mutagenicity Training set (n=111)

