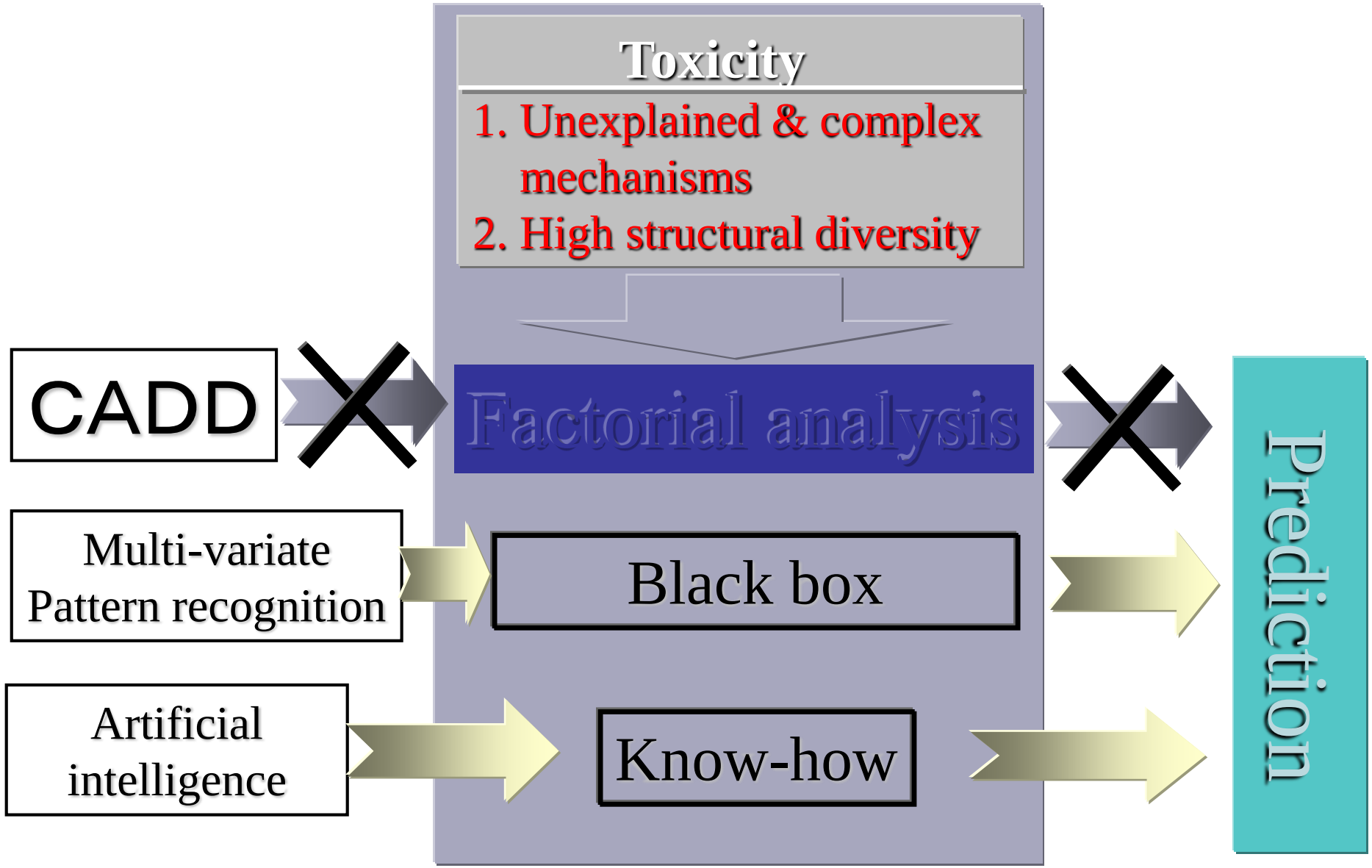
Development of "K-step Yard sampling method" and Apply to the ADME-T In Silico Screening

Kohtaro Yuta

1. Toxicity prediction and Pattern recognition (PR)
2. General features of data analysis by PR.
3. Building process to the features of “KY-method”
   *Step1 ;Yard sampling methods
   *Step2 ; K-step approach
   *Step3 ; Merge two approaches
   Yard sampling and K-step handling
4. Applicability statement of “KY-method”
   Classifying 7000 sample set of Ames test
5. Summary and conclusion

Approaches for toxicity screening



Problems of toxicity screening by pattern recognition

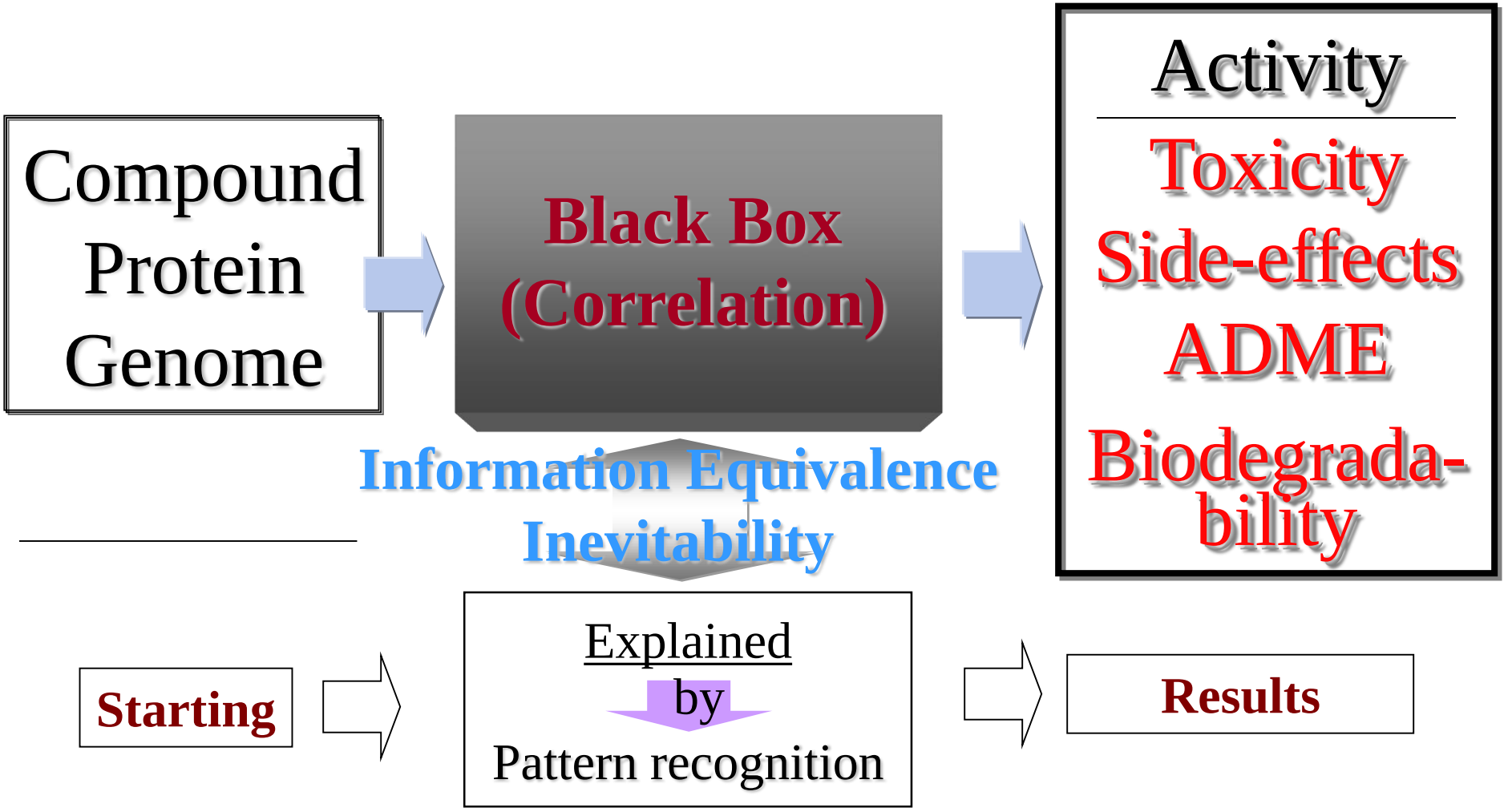
■ **Only a few methods can be applicable on toxicity screening**

Most of drug design methods can not be applied.

- **Un-known mechanisms →**
  Inability of "Hypothesis testing" method
- **Extremely high compounds diversity →**
  From methane to macrolide
- **Large sample population →**
  Normal D.D. approach handle small samples

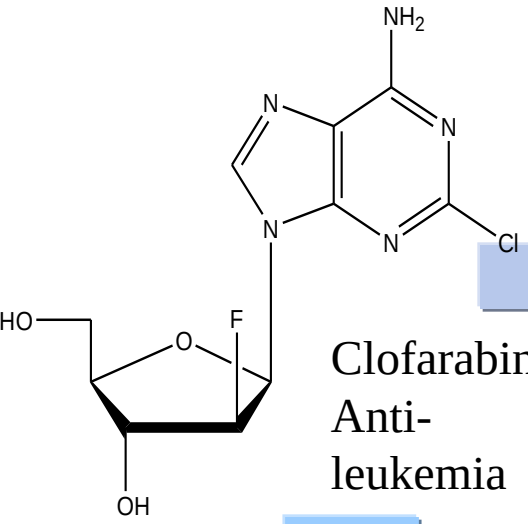
Basic concept of prediction by Pattern recognition

Principle of Information Equivalence



Basic concept of prediction by Pattern recognition

Principle of Information Equivalence



Clofarabin:
Anti-
leukemia

Black Box (Correlation)

Activity

Toxicity
Side-effects
ADME
Biodegrada-
bility

Information Equivalence
Inevitability

Initial Descriptors

MW
Atoms／Bonds
HOMO／LUMO
CPSS
Others

Feature Selection

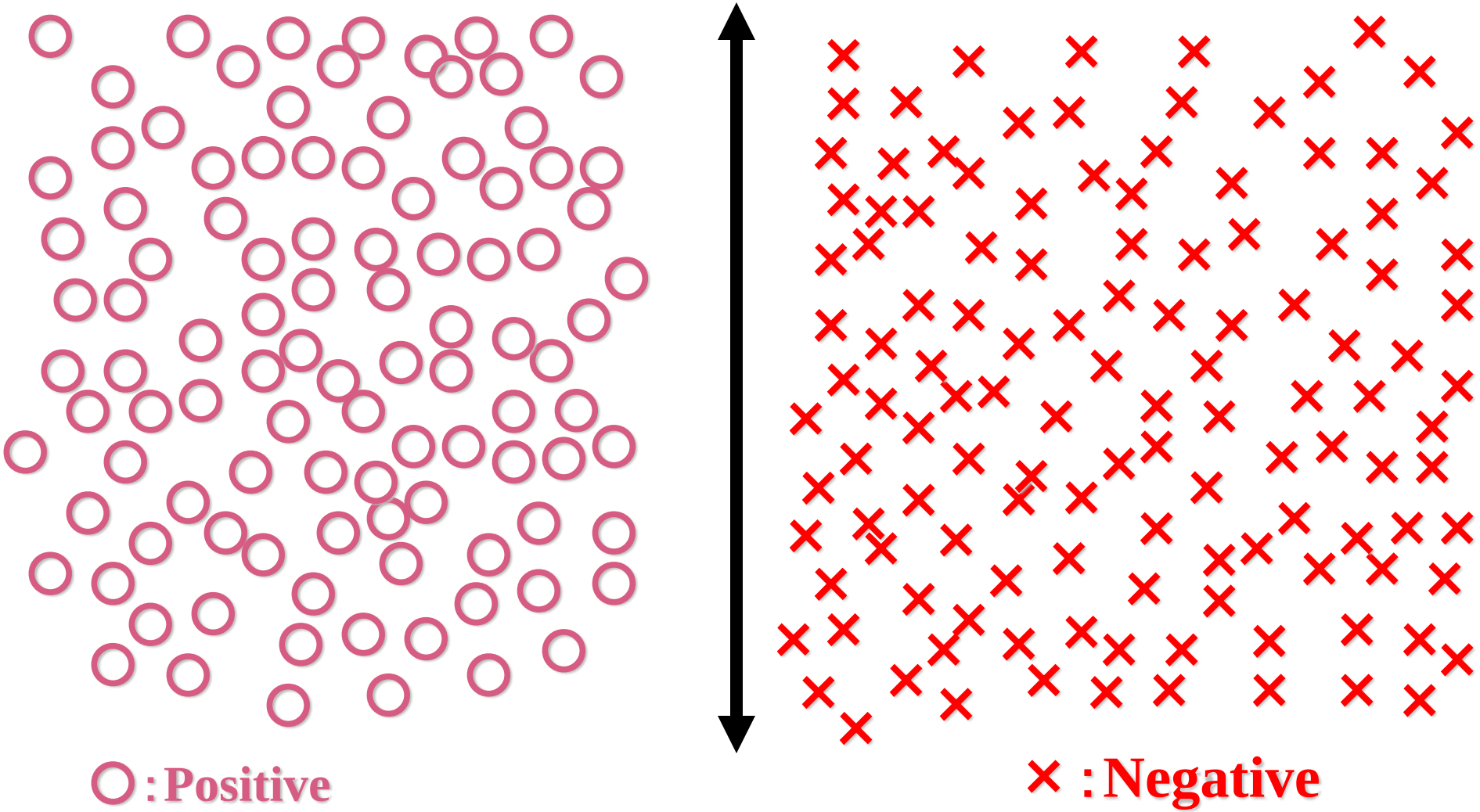
Final Descriptor Set

General features of data analysis by Pattern recognition techniques

Linear / Non-linear and DA / Fitting

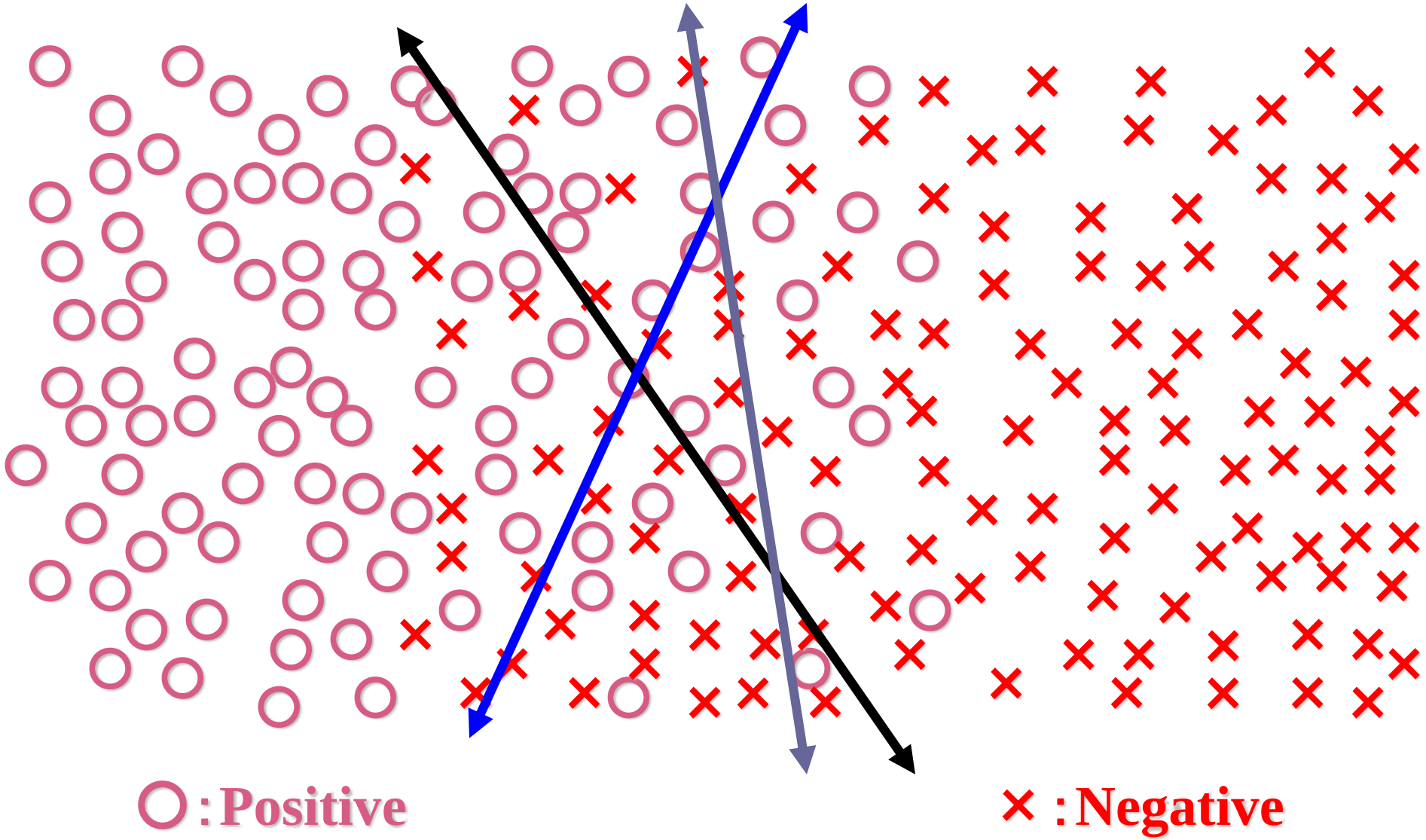
Sample space ：two cluster samples

Discriminant function for perfect classification



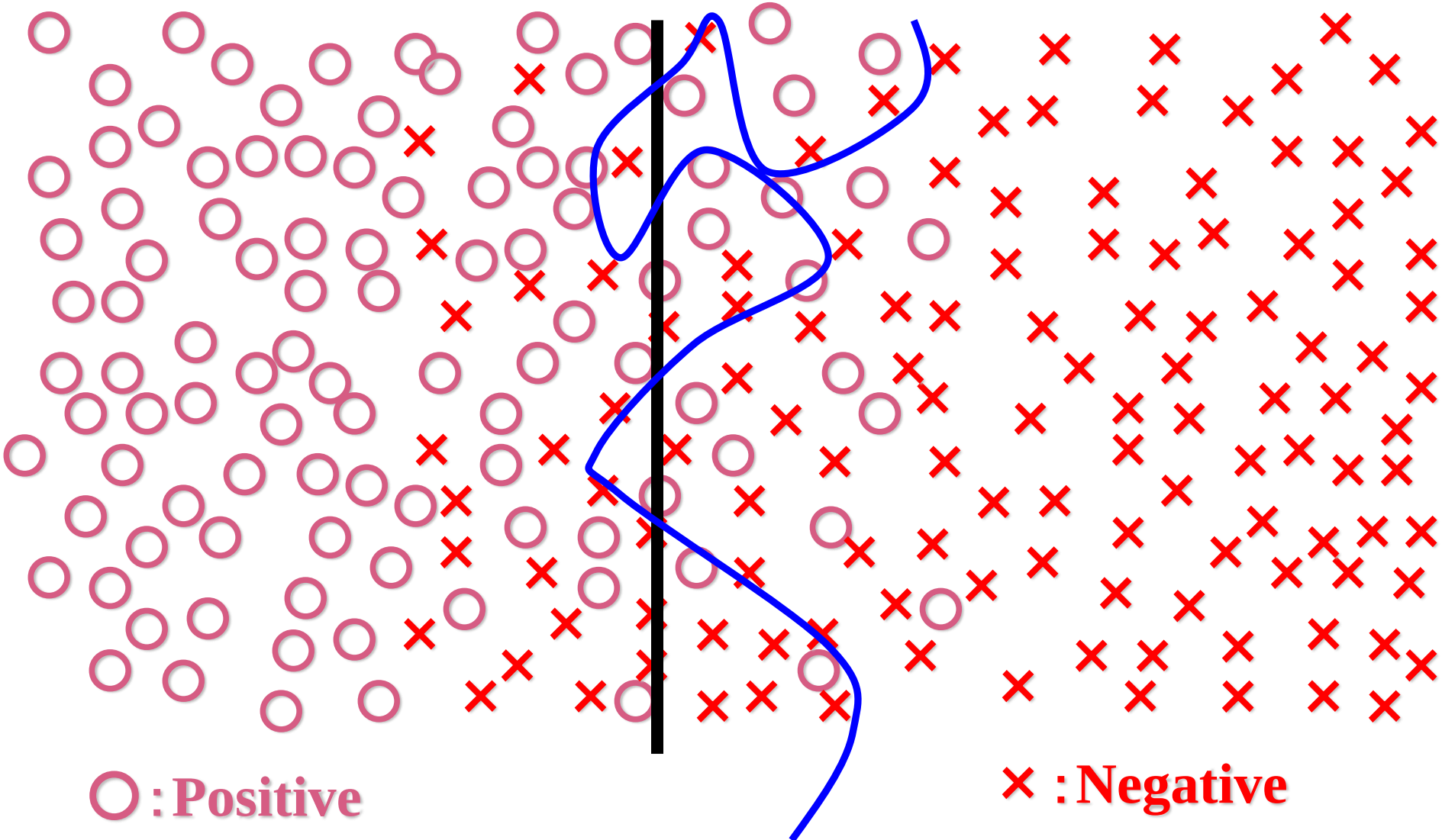
Sample space ：highly overlapped space

Discriminant function generated by various methods

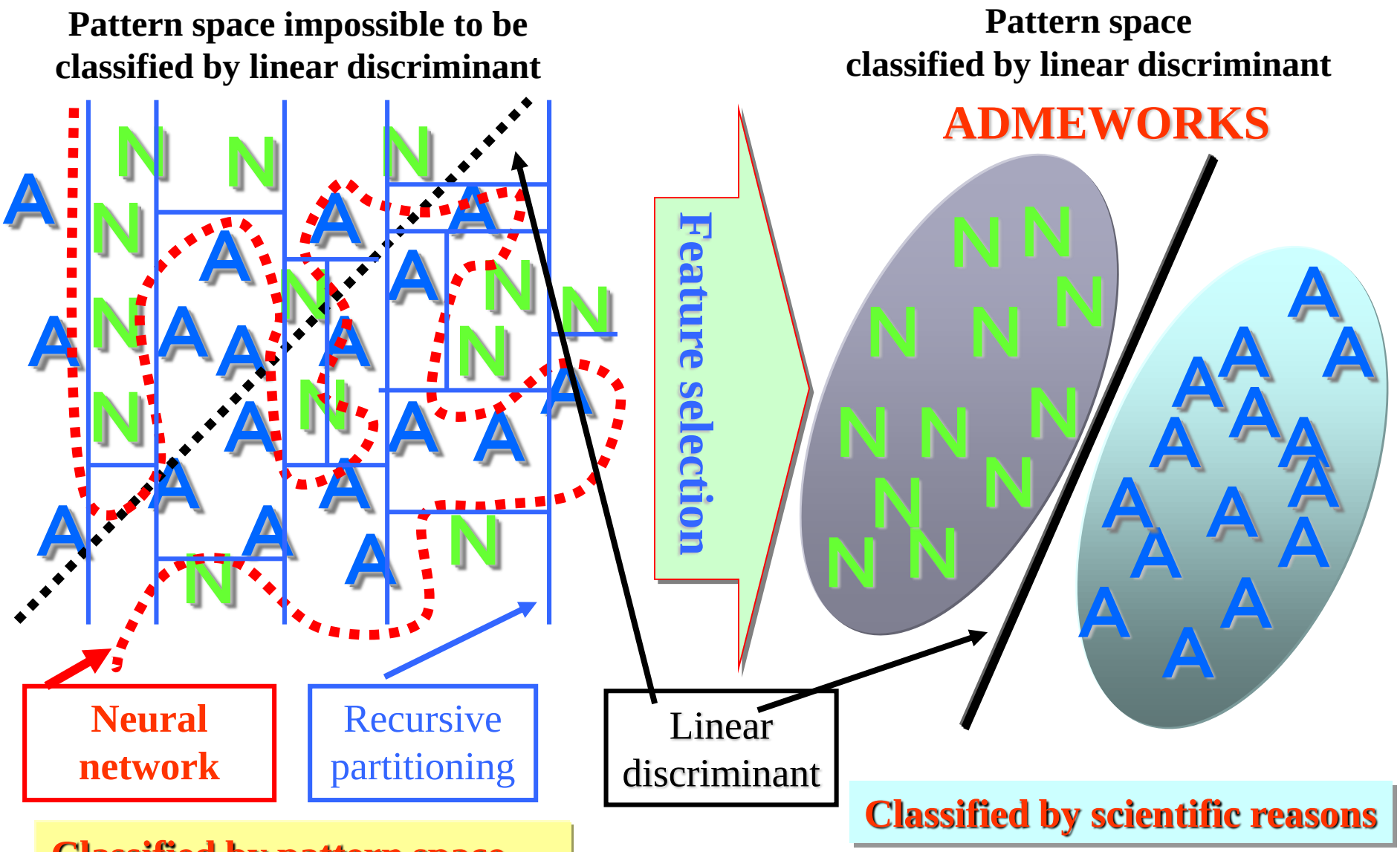


Sample space ：highly overlapped space

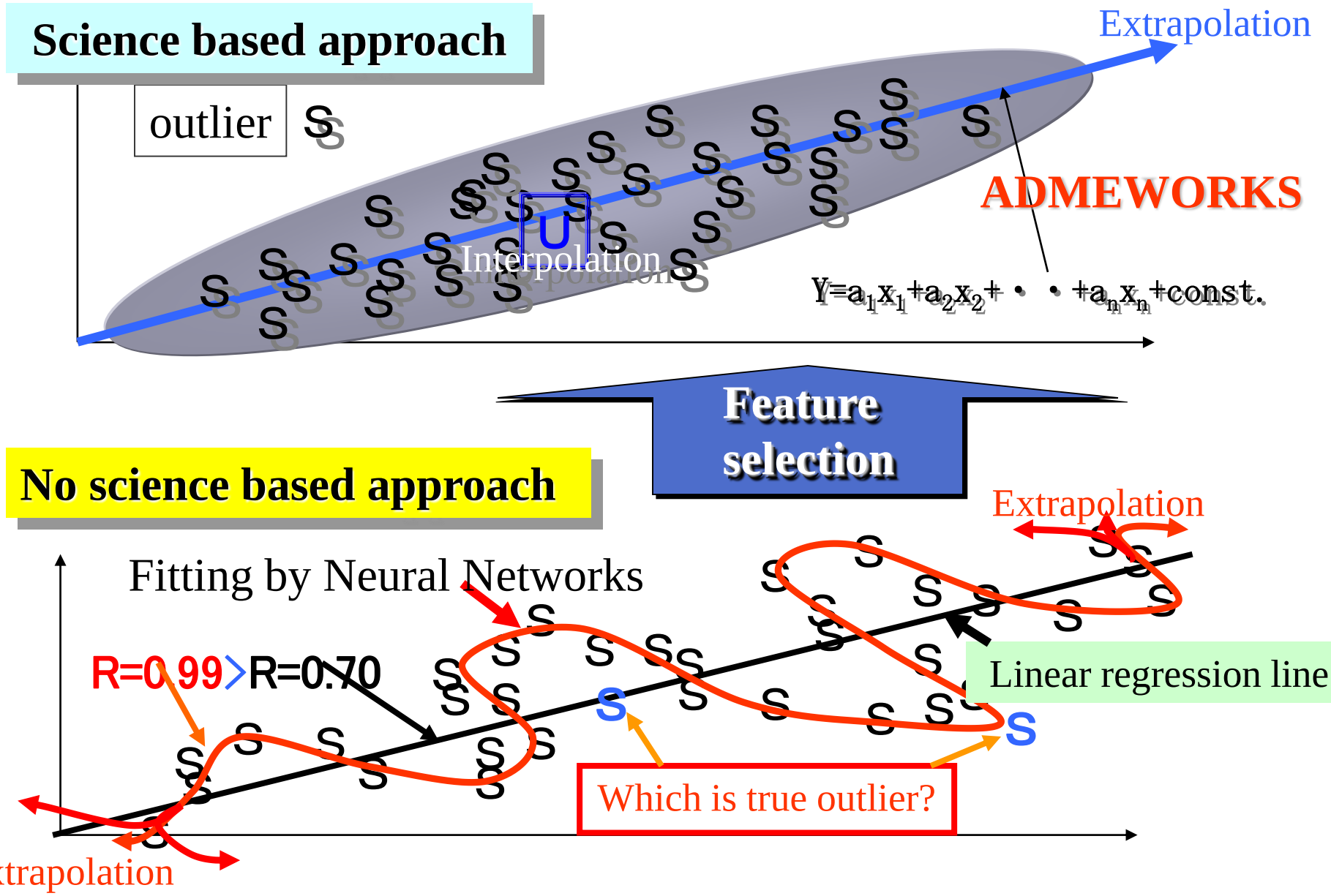
Discriminant function ： Linear and non-linear



Simple classification and scientific classification



Simple fitting and scientific fitting



☐Non-linear approach

Fit lines on existed sample space

No-remake sample space

Scientific approach

Remake sample space

Strong feature selection is required

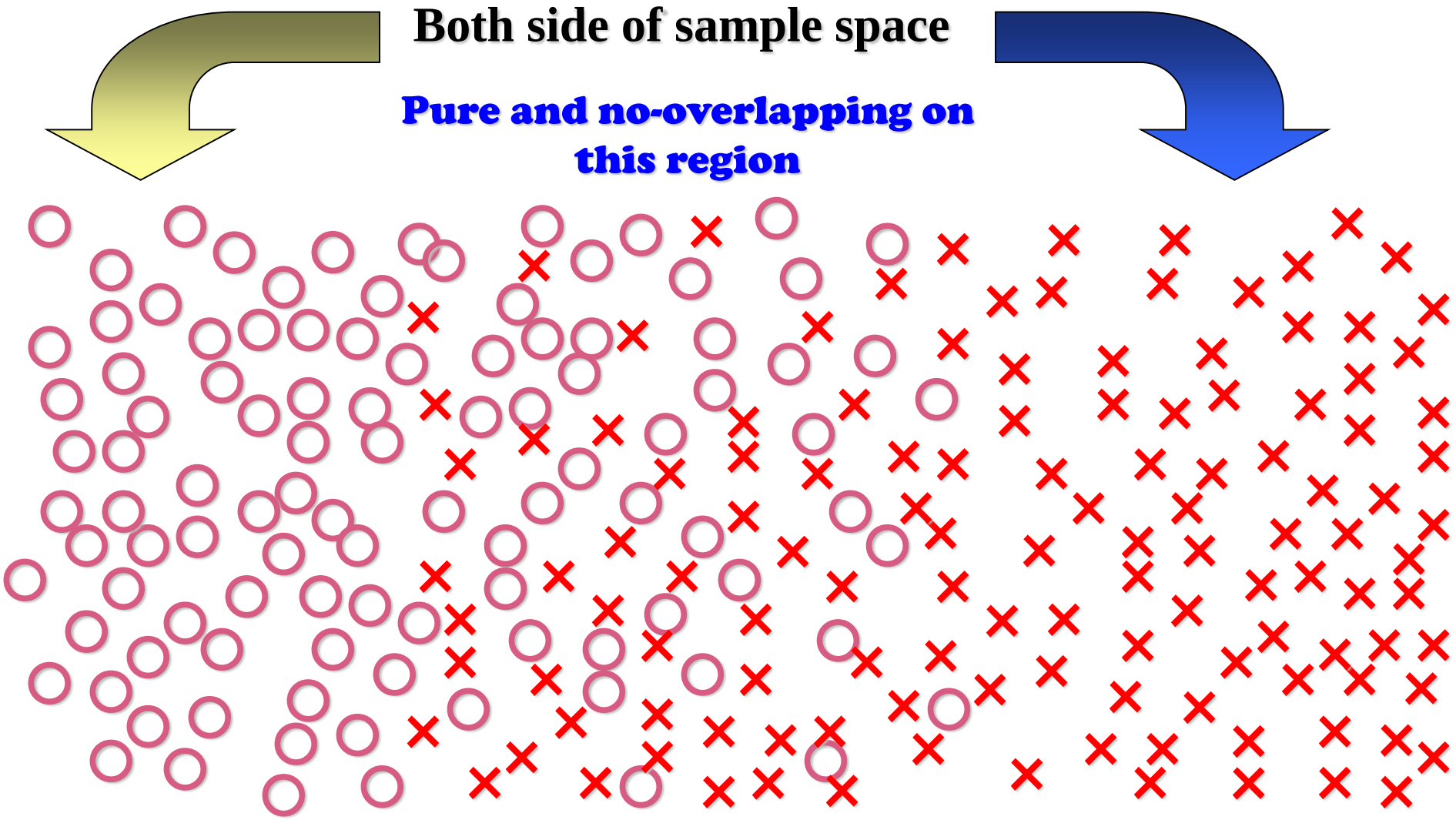
Fit samples for individual end point

☐Linear approach

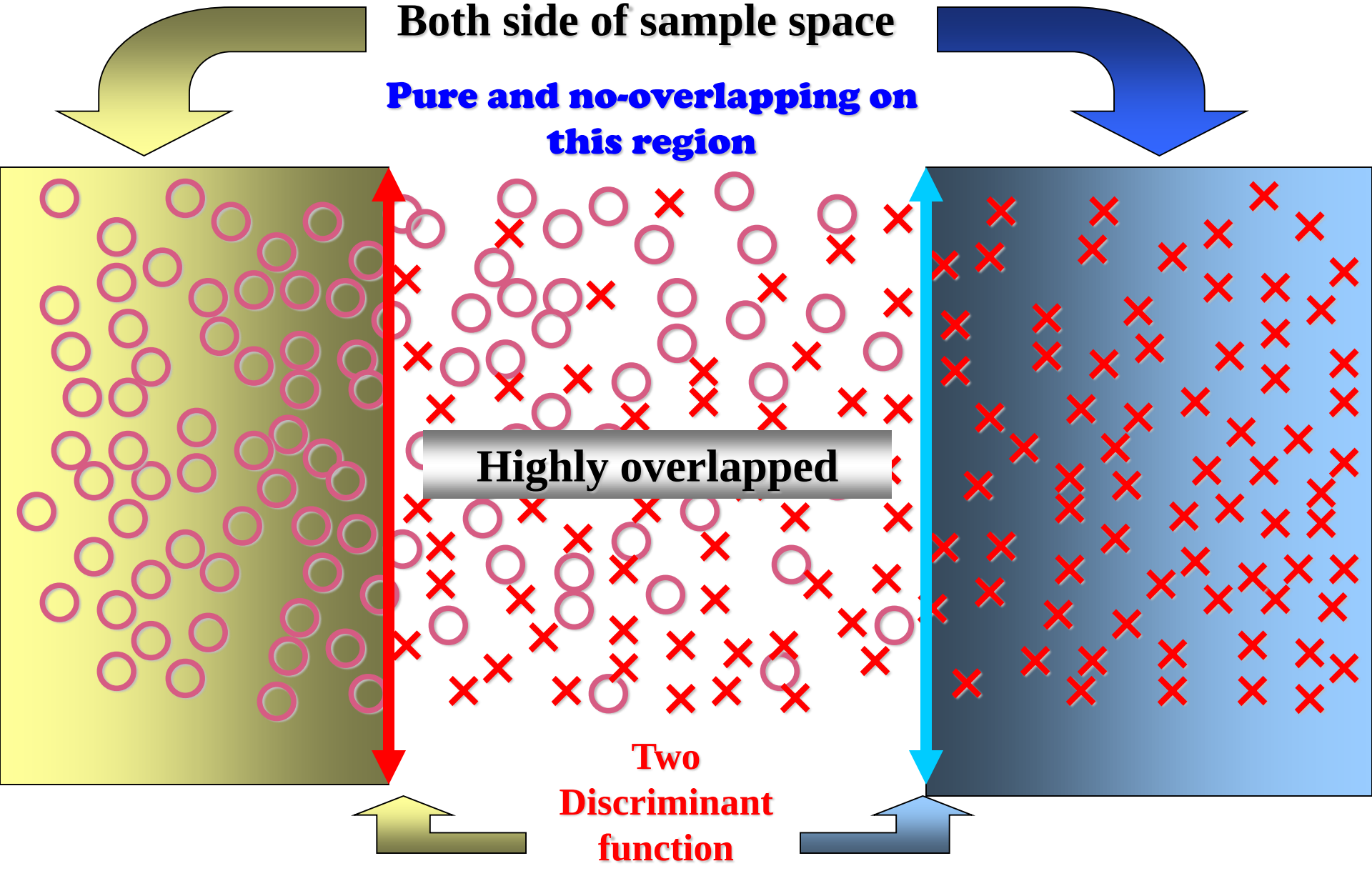
Building process to the features of "K-step Yard sampling method"

Step1: Yard sampling methods

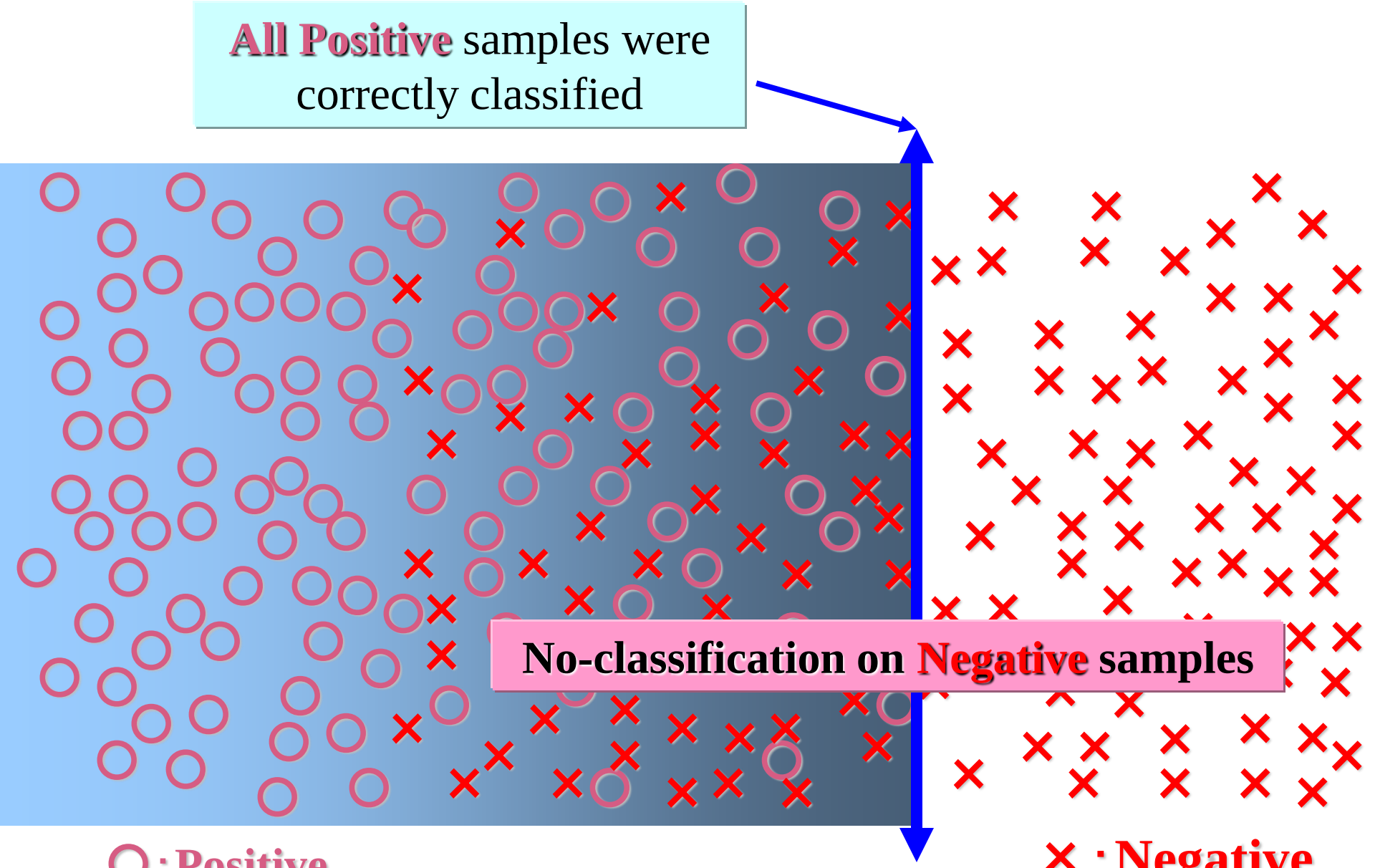
Spatial region on sample space



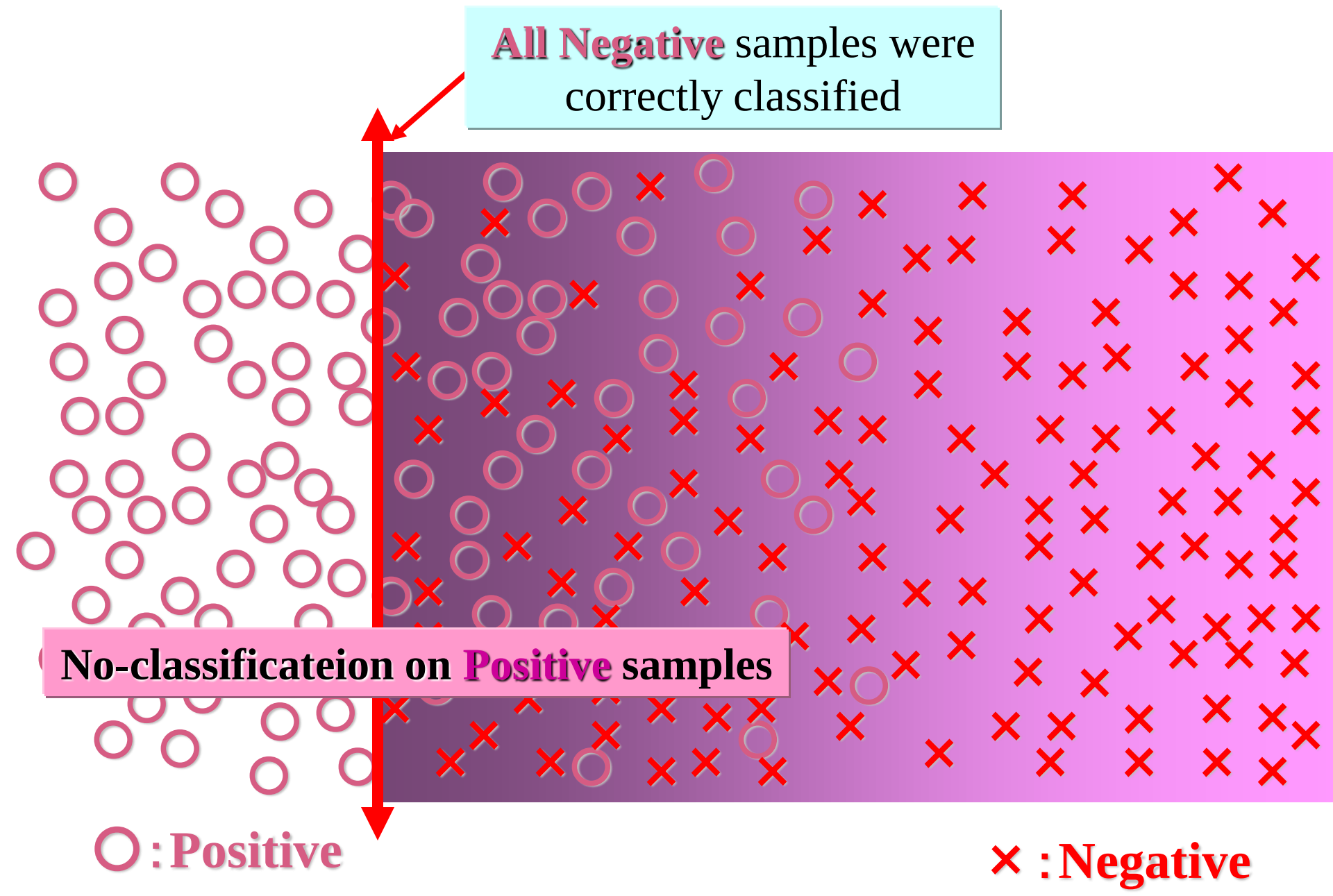
Spatial region on sample space



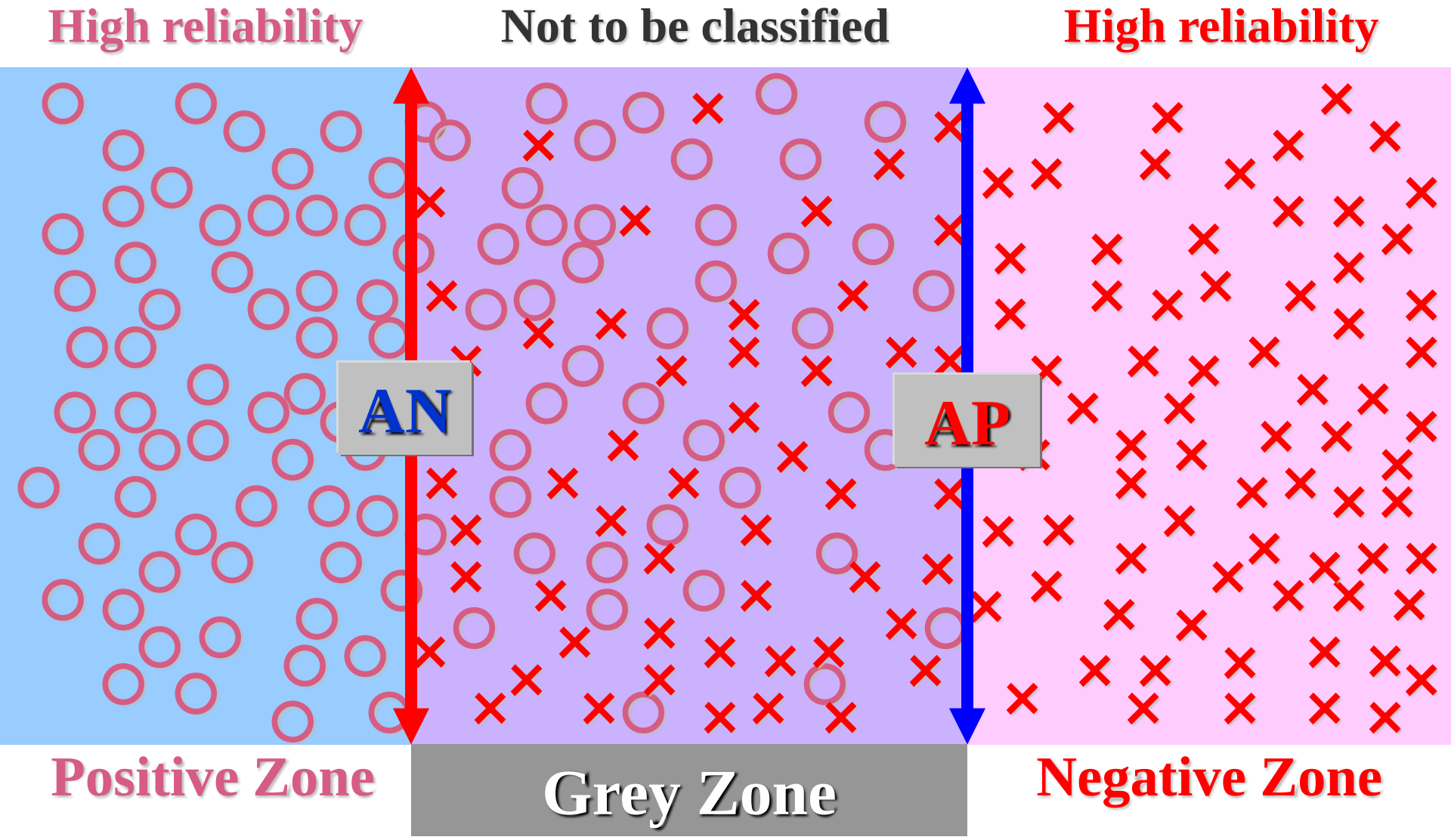
Property of AP（All Positive）model



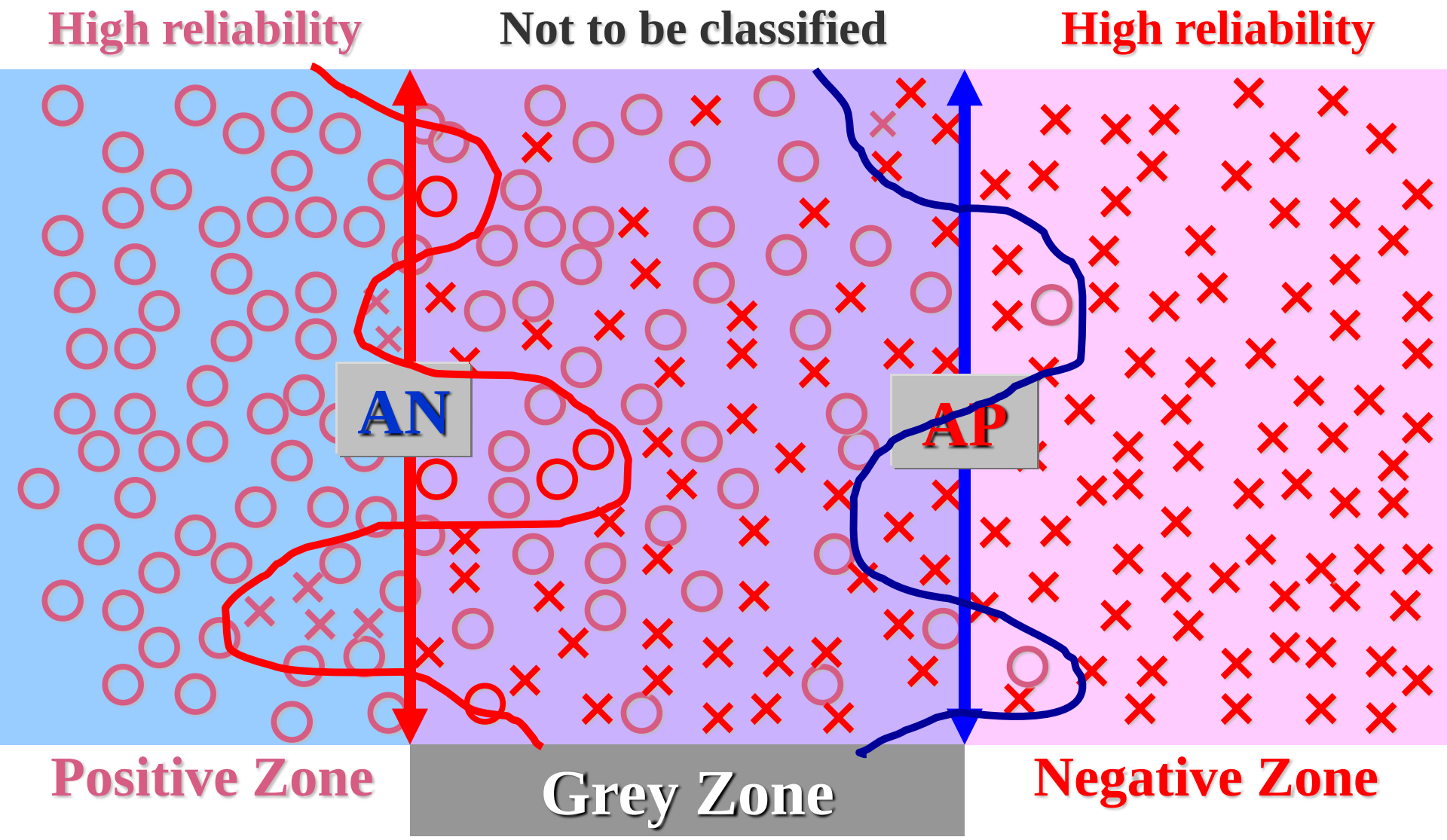
Property of AN（All Negative）model



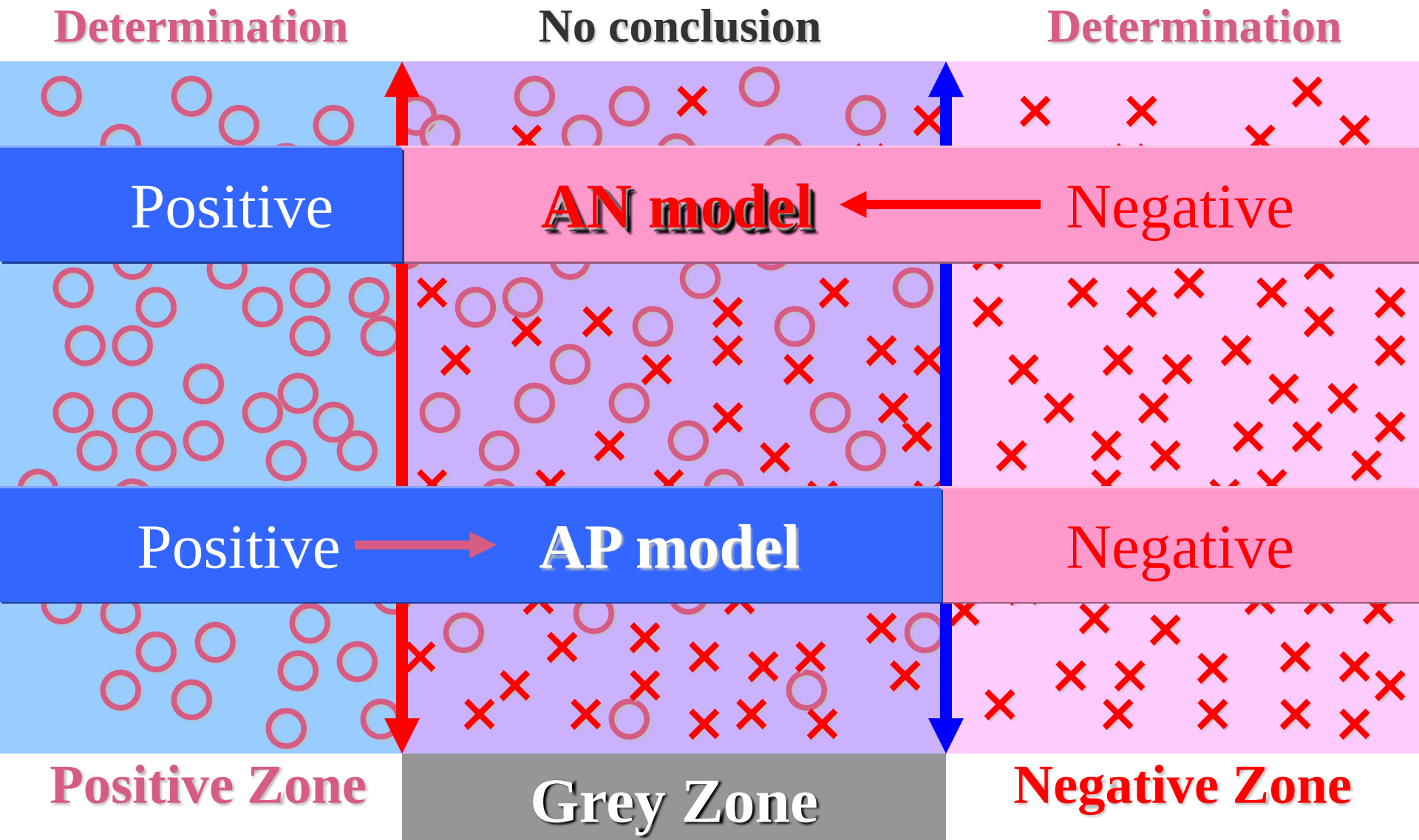
Combination of AN and AP models



Linear and non-linear discriminant on AP and AN models



Relations between Sample space & AN and AP models



Class determination by AN and AP models

- Sample Classification and prediction must be done by Combination of the results of AP and AN models.

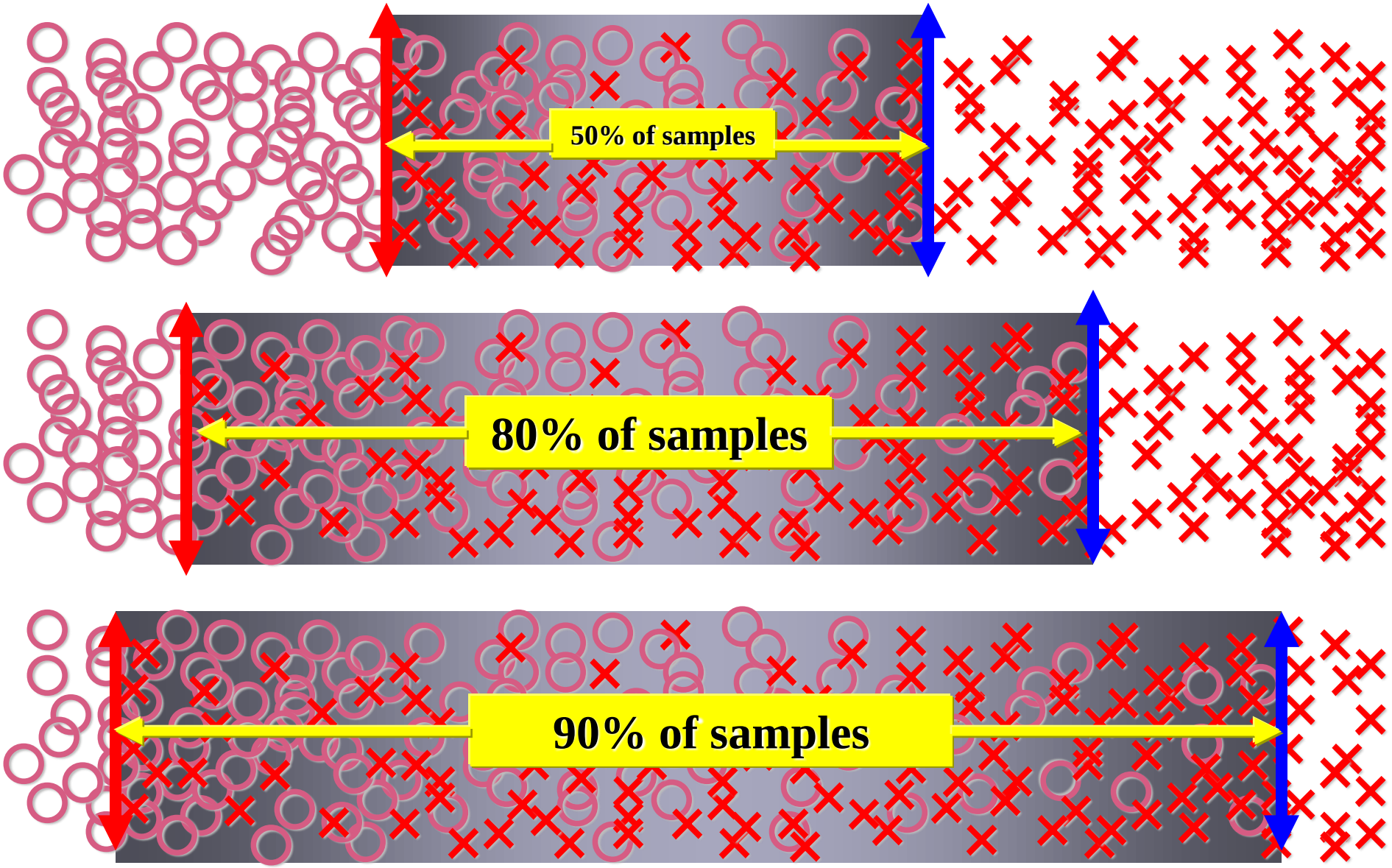
	AP model	AN model	Results
①	AP；POSI,	AN；POSI	→ POSI
②	AP；POSI,	AN；NEGA	→ GREY
③	AP；NEGA,	AN；POSI	→ GREY
④	AP；NEGA,	AN；NEGA	→ NEGA

Building steps to the features of "K-step Yard sampling method"

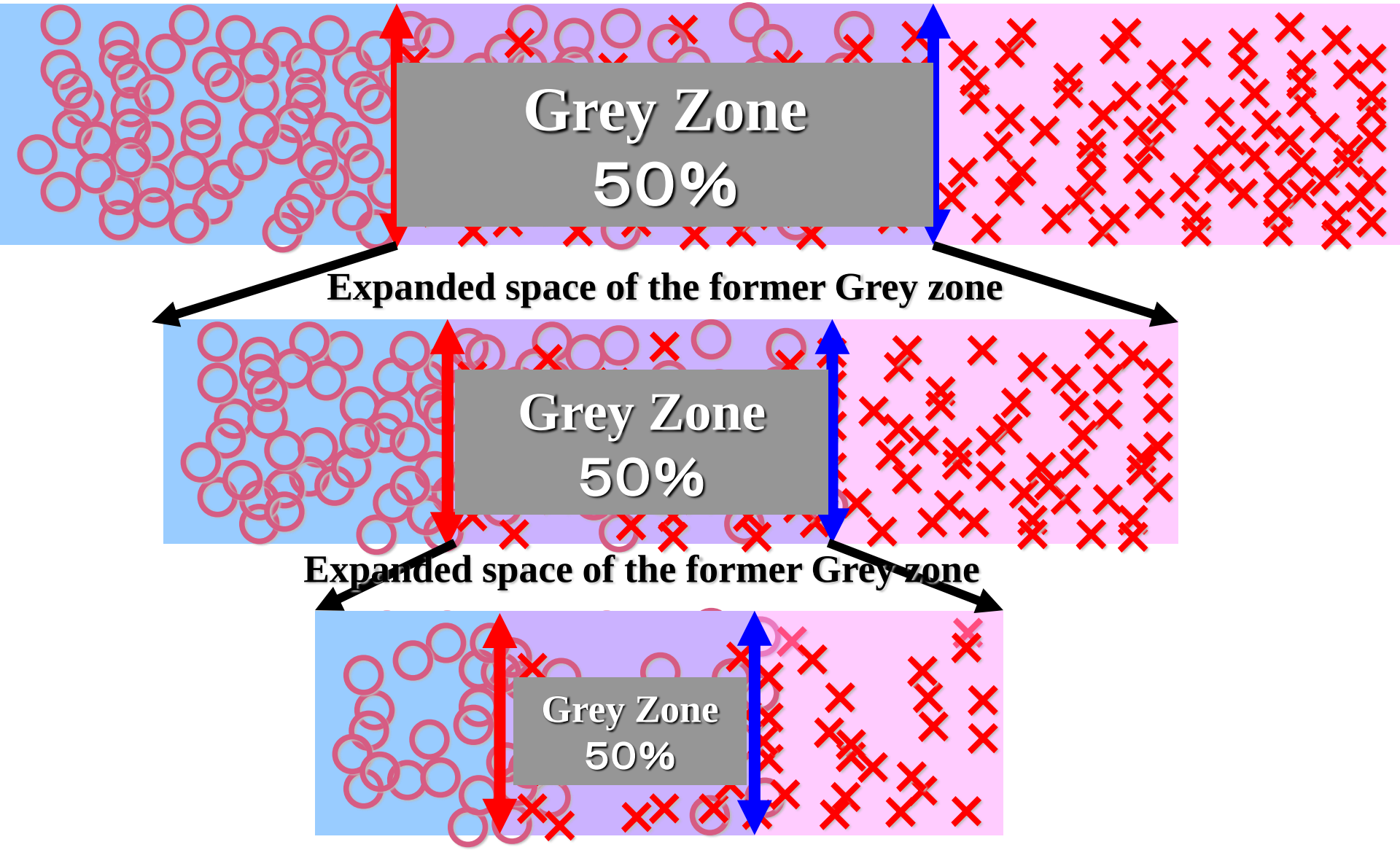
Step2: K-step approach

Problems of Yard sampling methods

The ratio of Grey zone:Highly overlapped sample space

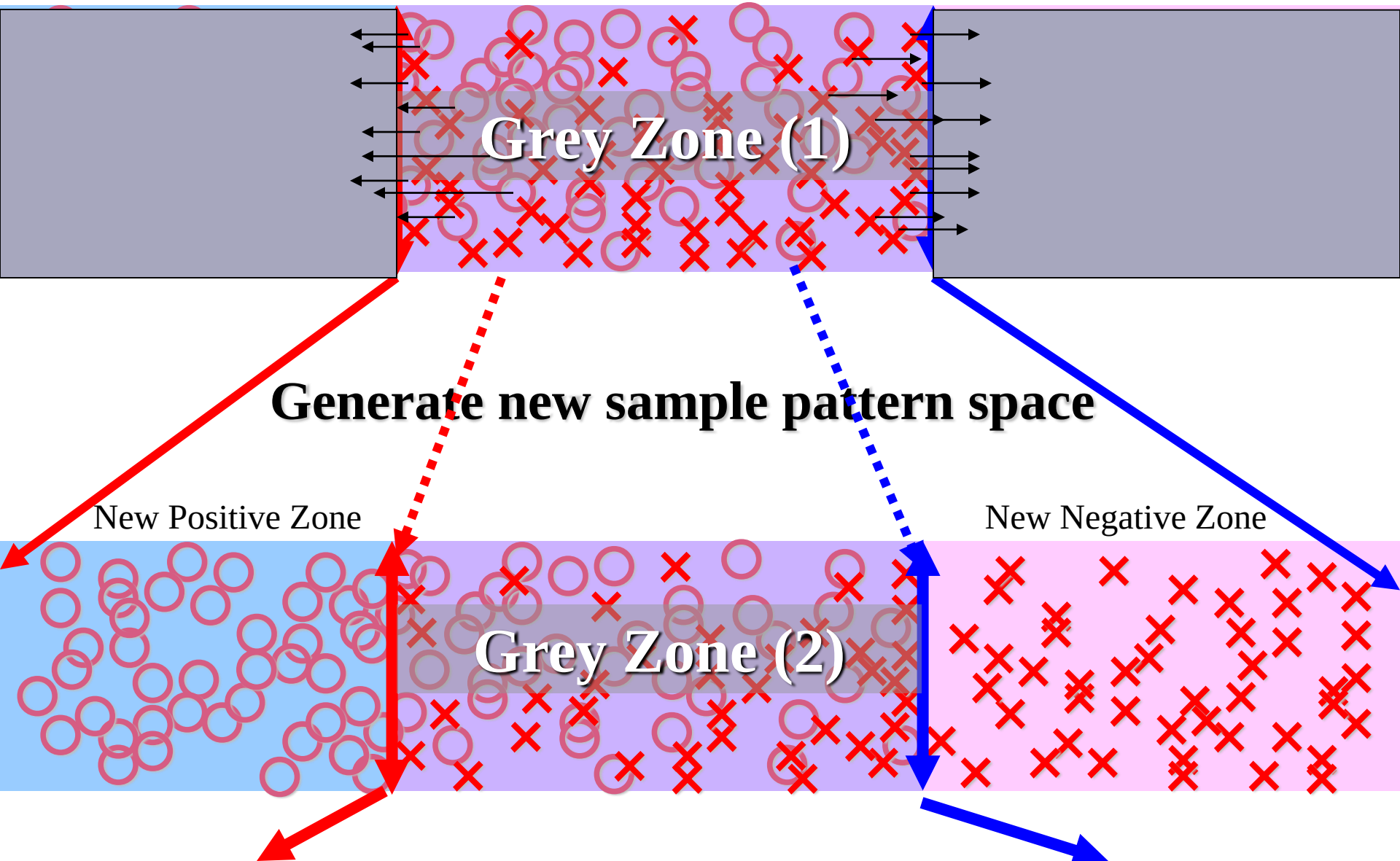


Steps to the K-step methods



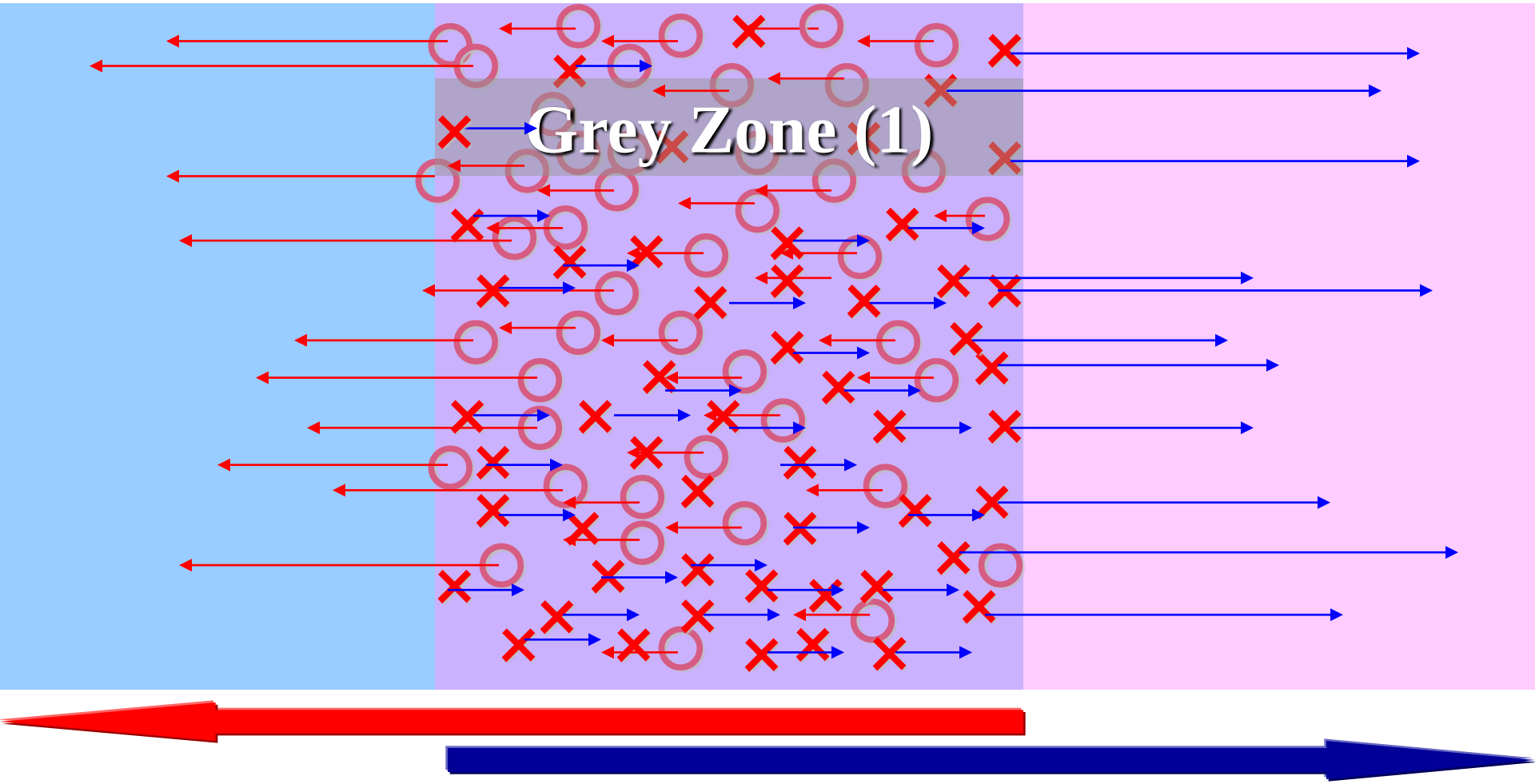
“K-step Yard sampling（KY）Method”

Improvement by repeated classification of Grey Zone samples



“K-step Yard sampling（KY）Method”

□ **Relocation of Grey Zone samples on new sample space**



Building steps to the features of "K-step Yard sampling method"

Step3: Merge two approaches: Yard sampling and K-step handling

The way to perfect classification

Partially realized by Yard sampling process

Not determined class on Grey zone compounds

Fixed up by K-step approach

Perfect classification for all samples:
any case, any time, any condition, others

“K-step Yard sampling” method

Yard sampling

process

For perfect classification

K-step

repeated processes

For no Grey zone

Applicability statement of "K-step Yard sampling method"

Classifying 7000 sample set of Ames test

Challenge for classification and prediction

K-step Yard sampling method

KY-method

The most powerful and advanced data analysis method

The most difficult classification problem

6,965 sample of Ames test samples were,

Classified perfectly

Application test of “K-step Yard sampling”

☐Samples

1. Ames test data
2. Sample population
   total :6,965
   Mutagen; 2,932
   Non-mutagen; 4,033

☐Result of KY-method

1. Number of steps : 23 steps ; 22 (2 models) + 1 (1 model)
2. Classification ratio : 100 %

☐Used system

ADMEWORKS / ModelBuilder
V 3.0.22

☐Used parameters (Initial condition)

Number of generated parameters : 838
Number of parameters for step 1 : 98
Confidency index (Samples(6965) / Parameters(98)) : 71.1 > 4.0

Application test by various D.A. methods

1. Linear discriminant analysis with linear least-squares method

Classification ratio : total; 73.50(6965), Mutagen;73.02(2932), Non mutagen;73.84(4033)
Number of mis-classified : (1846), (791) (1055)
Prediction ratio (L100 out) 72.58% deviance(0.92%)
(L500 out) 73.32% deviance(0.18%)

2. SVM (Support Vector Machine with Kernel)

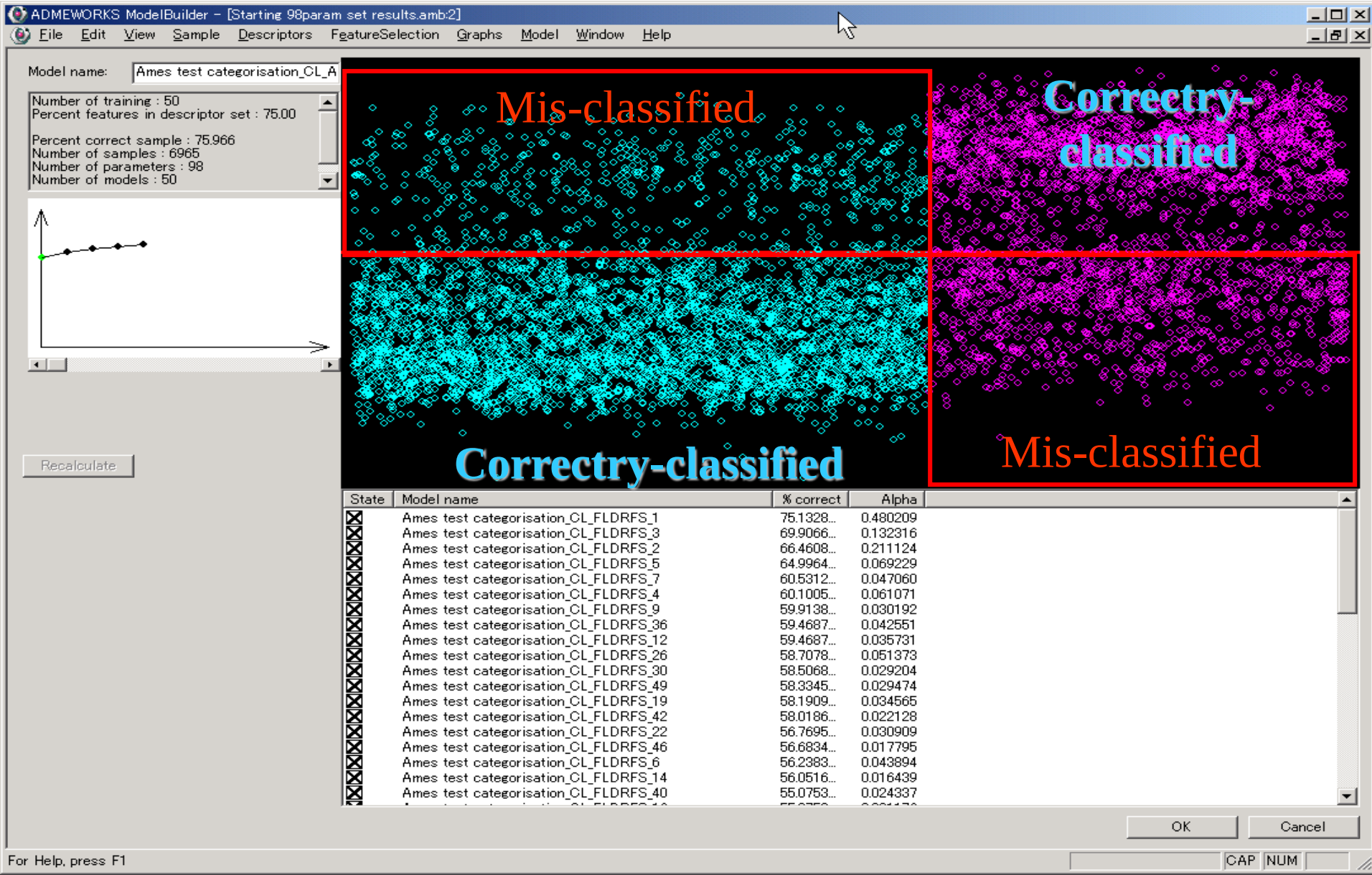
Classification ratio : total; 90.87(6965), Mutagen;86.83(2932) Non mutagen; 93.80(4033)
Number of mis-classified : (636), (386) (250)
Prediction ratio (L500 out) 80.99% deviance(9.88%)

3. AdaBoost

Classification ratio : total; 77.24(6965), Mutagen;66.13(2932) Non-mutagen; 85.32(4033)
Number of mis-classified : (1585) (993) (592)
Prediction ratio (L500 out) 75.16% deviance(2.08%)

Classification results by AdaBoost

Sample distribution of 6,965 of 77.24%



“K-step Yard sampling（KY）Method”

Total steps : 23 steps (2 models) + 1 step (1 model)

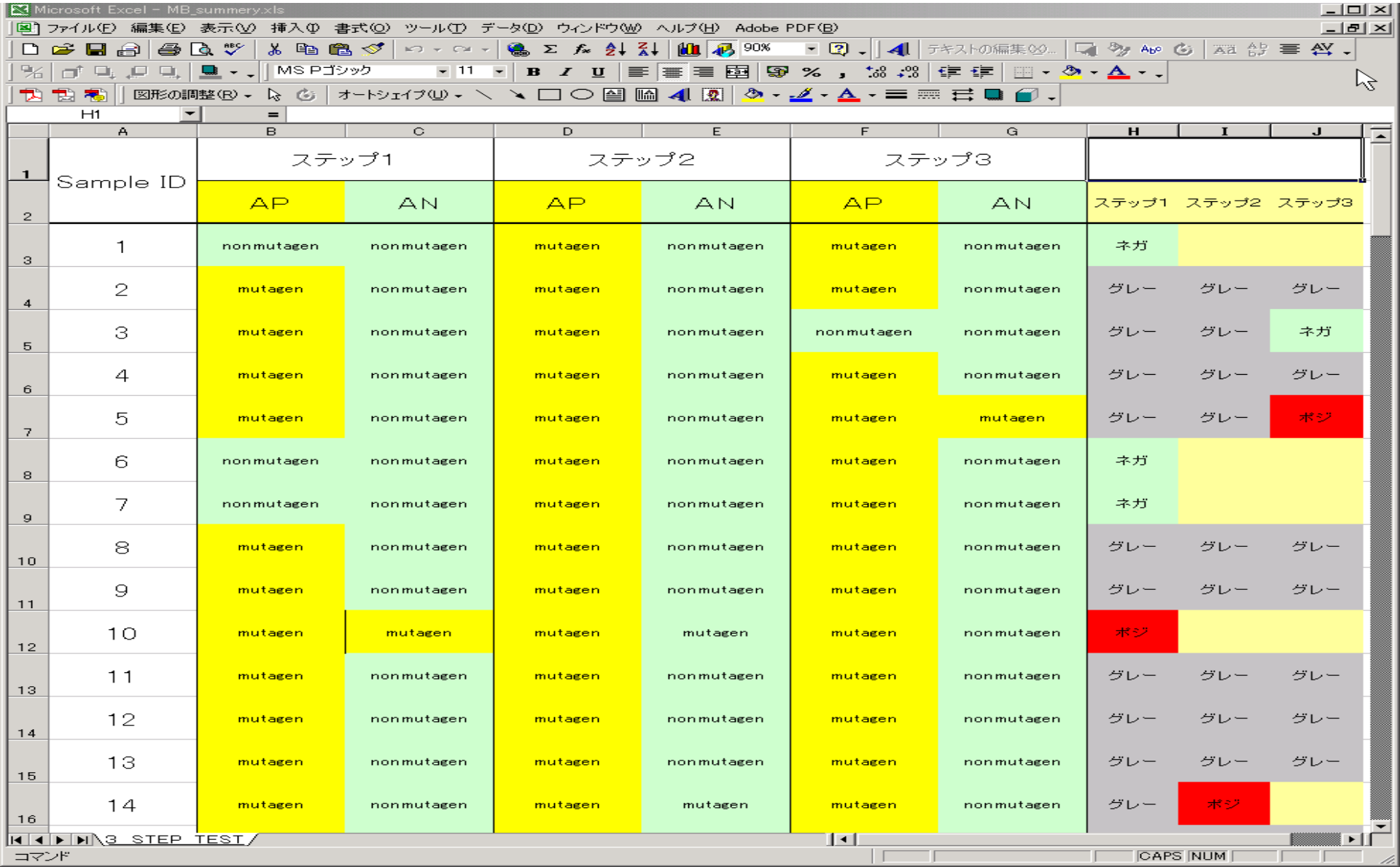
ステップID（KY法）	Starting samples(Total)	Mutagen (Initial)	Non-mutagen (Initial)	Grey sample (Initial)
	Final samples	Mutagen (Final)	Non-mutagen (Final)	Grey sample (Final)
	Determined samples(Total)	Determined samples(Mut.)	termined samples(Non-mu	Grey ratio(%) (Grey/Total)
1	6965	2932	4033	0
	5864	2413	3451	5864
	1101	519	582	84.19
2	5864	2413	3451	5864
	5108	2142	2966	5108
	756	271	485	87.11
3	5108	2142	2966	5108
	4486	1919	2567	4486
	622	223	399	87.82
4	4486	1919	2567	4486
	4133	1779	2354	4133
	353	140	213	92.13
5	4133	1779	2354	4133
	3794	1651	2143	3794
	339	128	211	91.8
6	3794	1651	2143	3794
	3462	1485	1977	3462
	332	166	166	91.25
7	3462	1485	1977	3462
	3090	1345	1745	3090
	372	140	232	89.25
8	3090	1345	1745	3090
	2826	1220	1606	2826
	264	125	139	91.46
9	2826	1220	1606	2826
	2592	1139	1453	2592
	234	81	153	90.63
10	2592	1139	1453	2592
	2384	1047	1337	2384
	208	92	116	91.98

“K-step Yard sampling（KY）Method”

12	2095	931	1164	2095
	1848	829	1019	1848
	247	102	145	88.21
13	1848	829	1019	1848
	1607	733	874	1607
	241	96	145	86.96
14	1607	733	874	1607
	1380	623	757	1380
	227	110	117	85.87
15	1380	623	757	1380
	1028	466	562	1028
	352	157	195	74.49
16	1028	466	562	1028
	787	358	429	787
	241	108	133	76.56
17	787	358	429	787
	529	234	295	529
	258	124	134	67.22
18	529	234	295	529
	392	201	191	392
	137	33	104	74.1
19	392	201	191	392
	279	141	138	279
	113	60	53	71.17
20	279	141	138	279
	184	105	79	184
	95	36	59	65.95
21	184	105	79	184
	112	66	46	112
	72	39	33	60.87
22	112	66	46	112
	66	39	27	66
	46	27	19	58.93
23(1 model)	66	39	27	66
	0	0	0	0
	66	39	27	0

“K-step Yard sampling（KY）Method”

Classification results by 3 steps



Sample ID	ステップ1		ステップ2		ステップ3				
	AP	AN	AP	AN	AP	AN	ステップ1	ステップ2	ステップ3
1	nonmutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	ネガ		
2	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	グレー	グレー	グレー
3	mutagen	nonmutagen	mutagen	nonmutagen	nonmutagen	nonmutagen	グレー	グレー	ネガ
4	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	グレー	グレー	グレー
5	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	mutagen	グレー	グレー	ポジ
6	nonmutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	ネガ		
7	nonmutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	ネガ		
8	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	グレー	グレー	グレー
9	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	グレー	グレー	グレー
10	mutagen	mutagen	mutagen	mutagen	mutagen	nonmutagen	ポジ		
11	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	グレー	グレー	グレー
12	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	グレー	グレー	グレー
13	mutagen	nonmutagen	mutagen	nonmutagen	mutagen	nonmutagen	グレー	グレー	グレー
14	mutagen	nonmutagen	mutagen	mutagen	mutagen	nonmutagen	グレー	ポジ	

Spatial features of "K-step Yard sampling"

☐Summary

■Advantages

1. Sample number free approach

2. Sample distribution free approach

3. Perfect classification is achieved in any condition

■Disadvantages

1. Relatively complex operation to generate discriminant functions

2. Need powerful computer power


In Silico Data
Miracles by the KY-methods