The Chemical Senses – Eye Irritation, Nasal Pungency and Odor Thresholds

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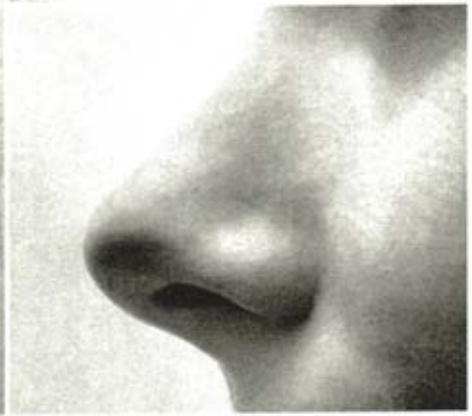
The Five Senses

Touch

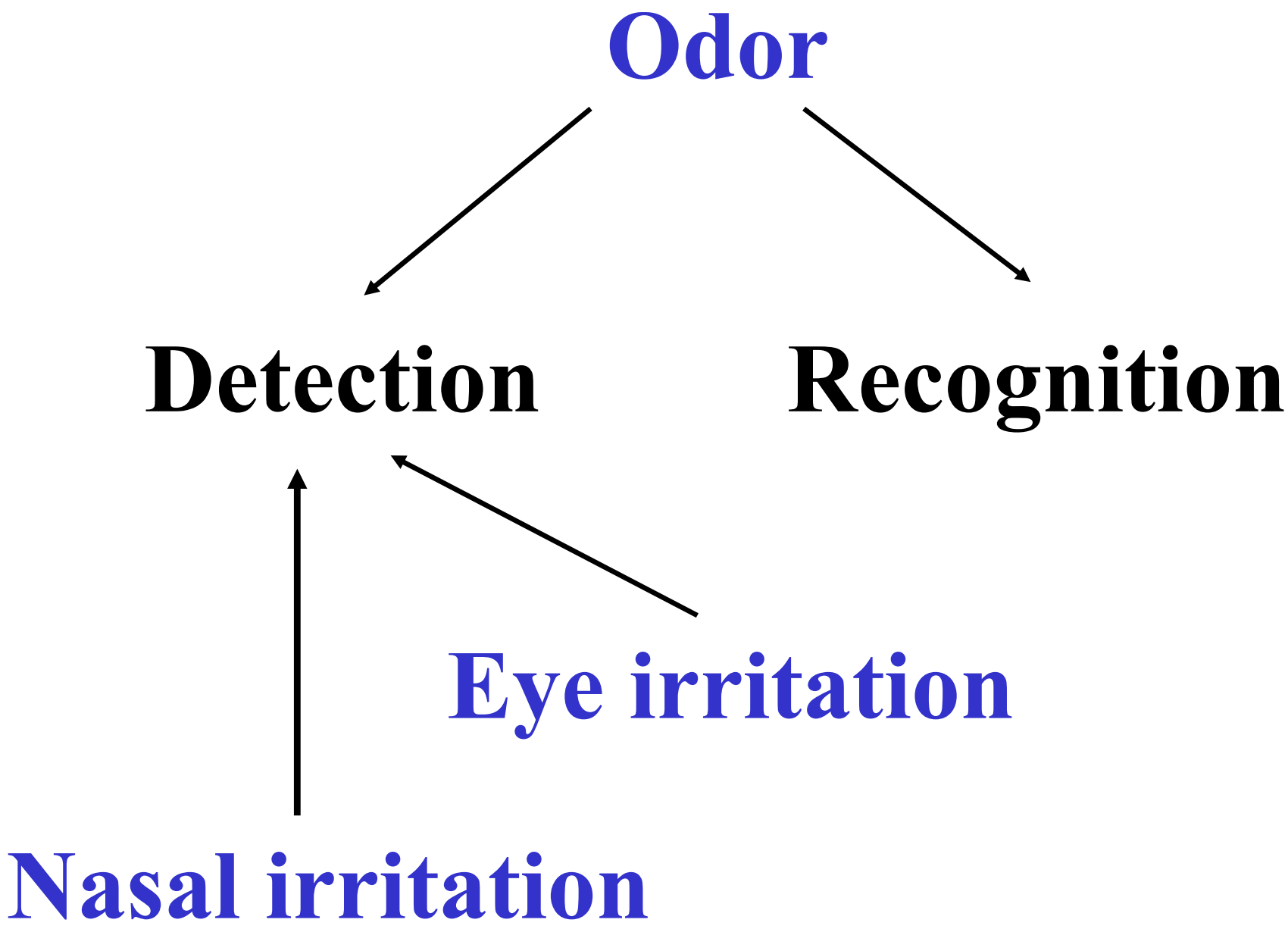
Taste

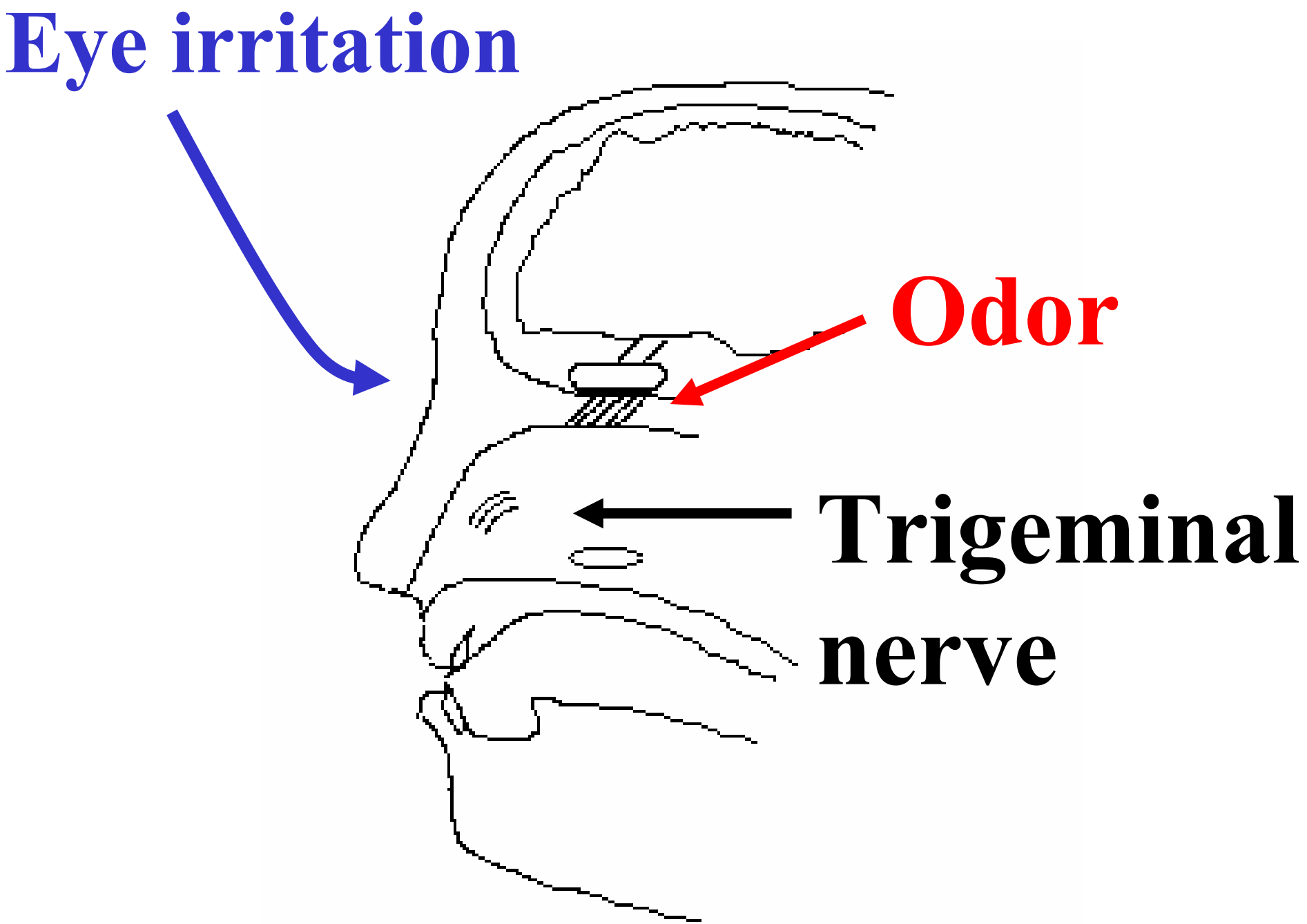
Sight



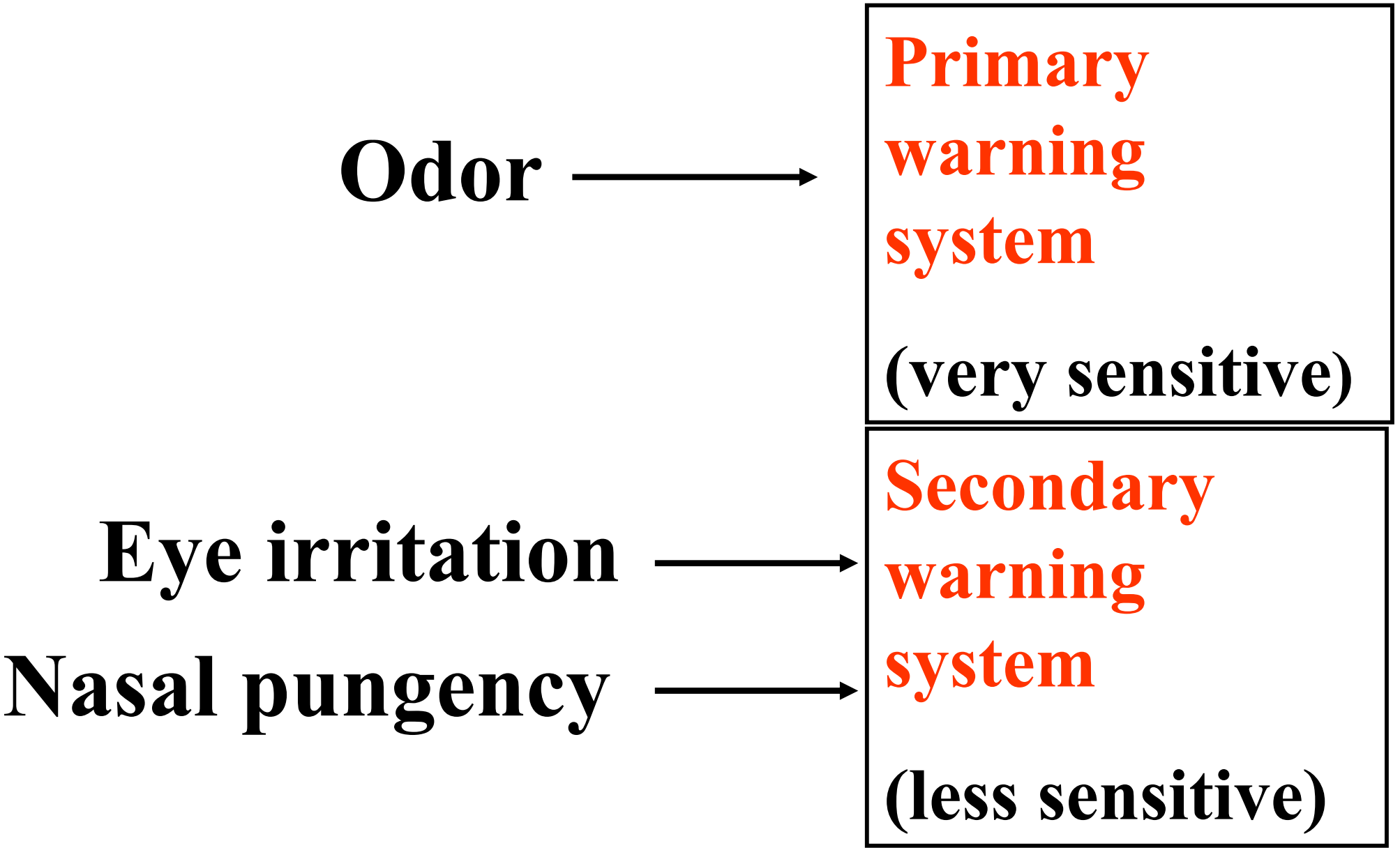
Smell

Sound


Odor
Detection
Recognition
Eye irritation
Nasal irritation


Eye irritation
Odor
Trigeminal nerve

The Chemical Senses



Indoor and Outdoor Air Concentrations

Volatile Organic Compounds, VOCs

Indoor concentrations greater by factors of about 7

How much time do we spend indoors ?

85 to 90 % indoors

Daily Exposure Ratios for VOCs

Indoor/Outdoor ~ 60

Volatile Organic Compounds, VOCs

- **Terpentine, white spirit**
- **Paints, lacquers, glues (carpets)**
- **Nail varnish - removers**
- **Tobacco smoke**

Perceived Effects of VOCs

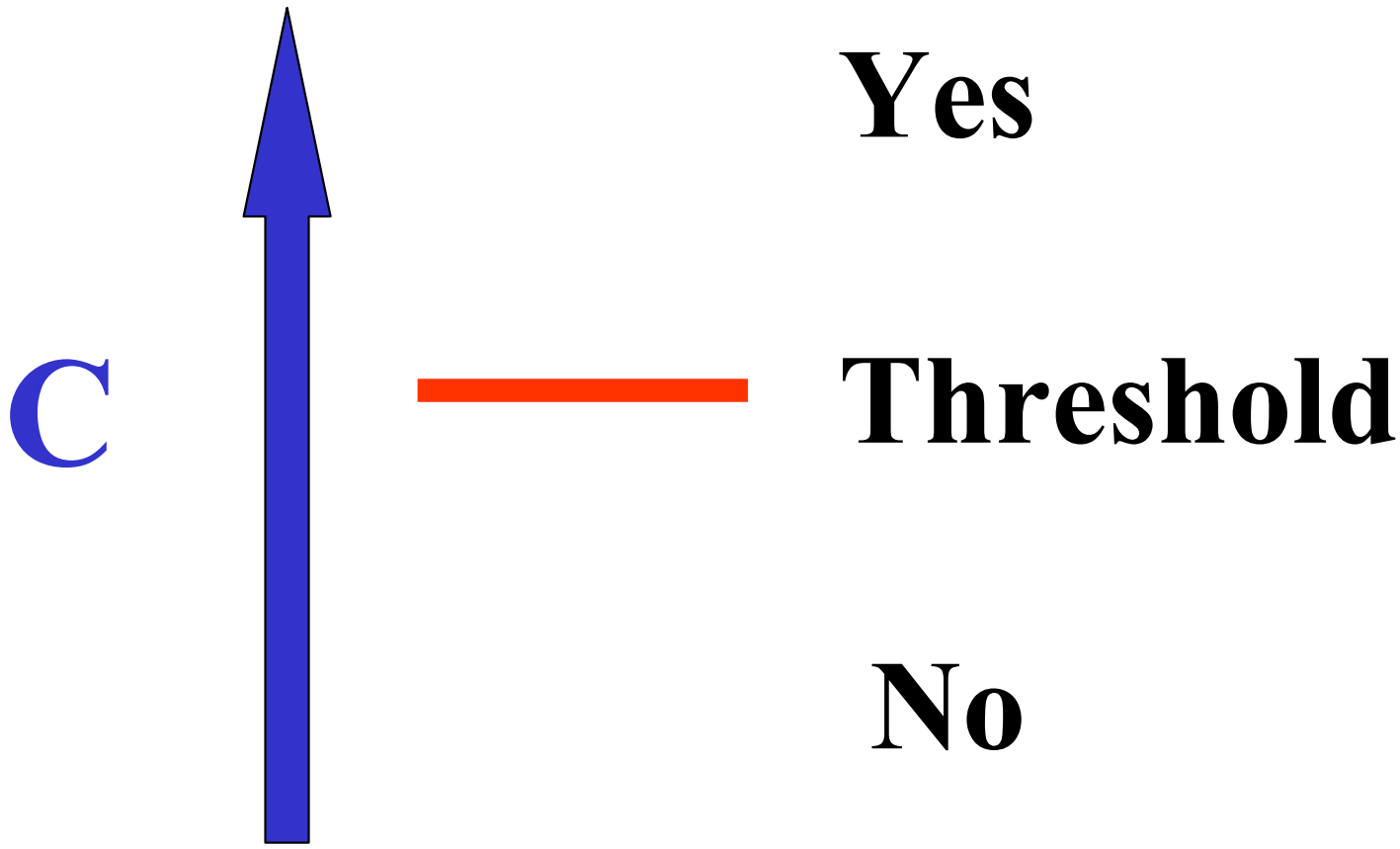
- **Headache**
- **Sore throat**
- **Eye irritation**
- **Smells**

Measures of Effects

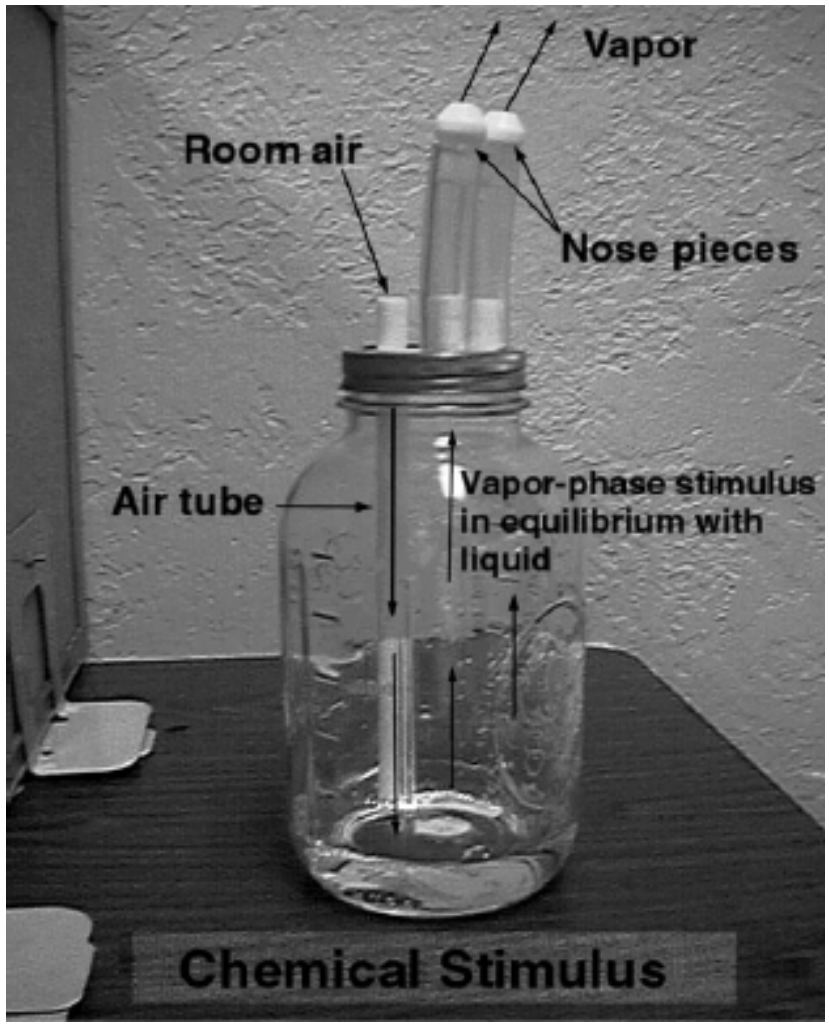
Threshold values

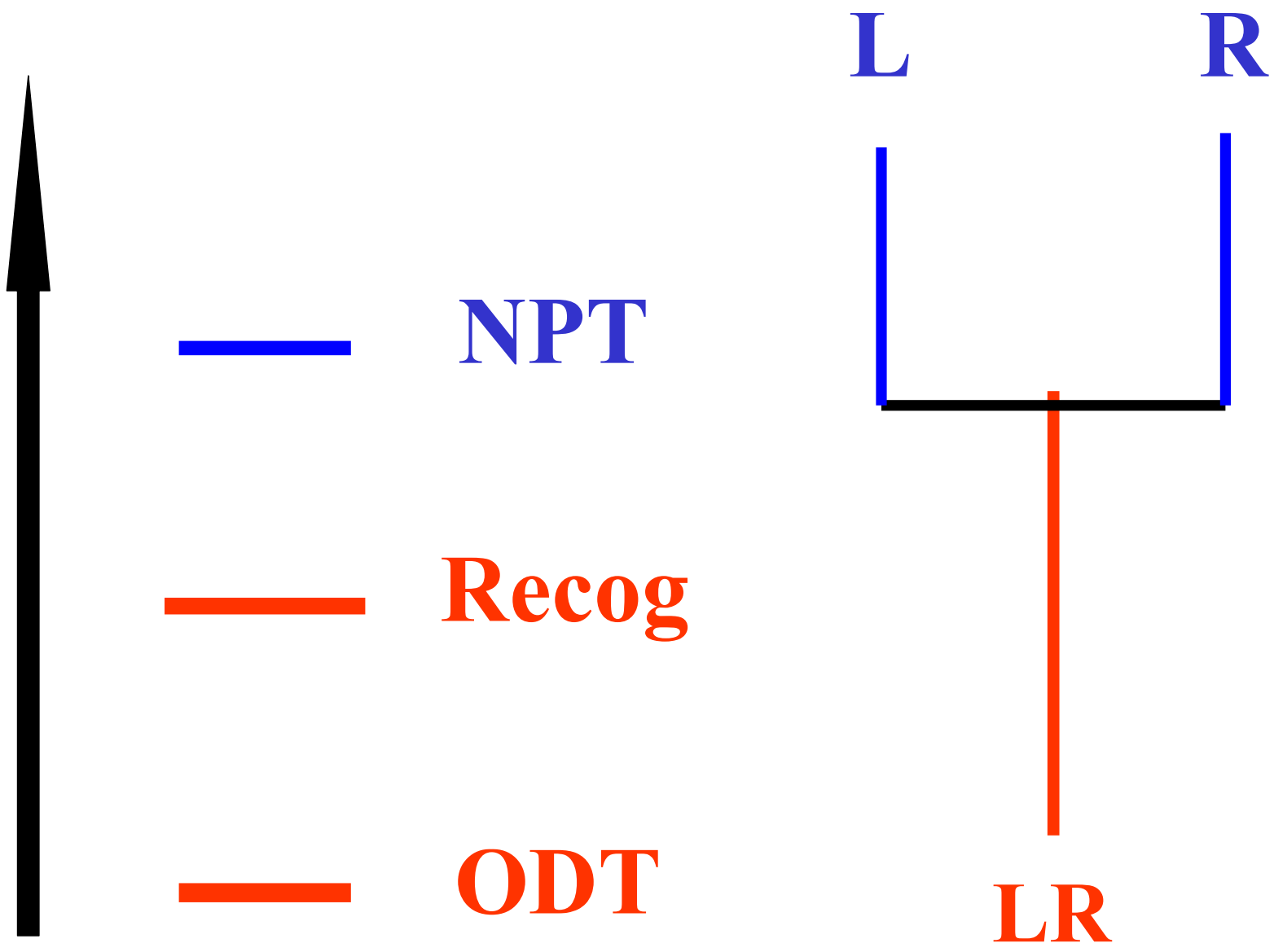
Odor	**ODT**
Nasal pungency	**NPT**
Eye irritation	**EIT**

Threshold Values



Procedure to obtain NPT values

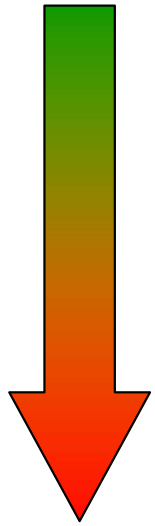



L
R
NPT
Recog
ODT
LR

- **VOCs - Odor more sensitive by factor of 500 than nasal pungency or eye irritation**
- **Odor - Can detect 1 part in 100,000 for VOCs**
- **For pheromones, 1 part in 100 million**

Some threshold values in ppm

Stimulus	NPT	ODT
Acetone	132000	11800
Ethanol	9000	70
Acetic acid	42	0.01



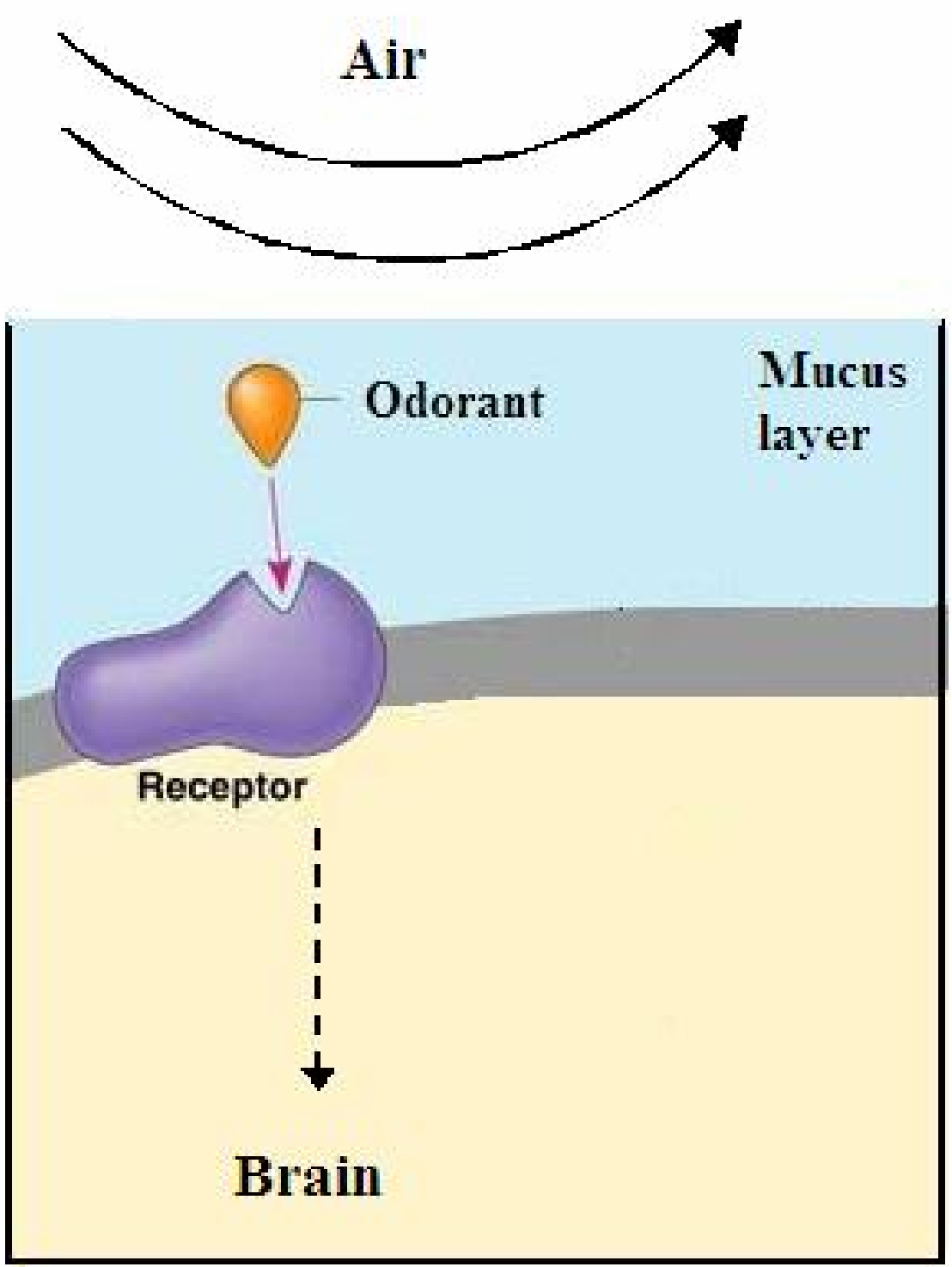
Potent

VOCs - How Many ?

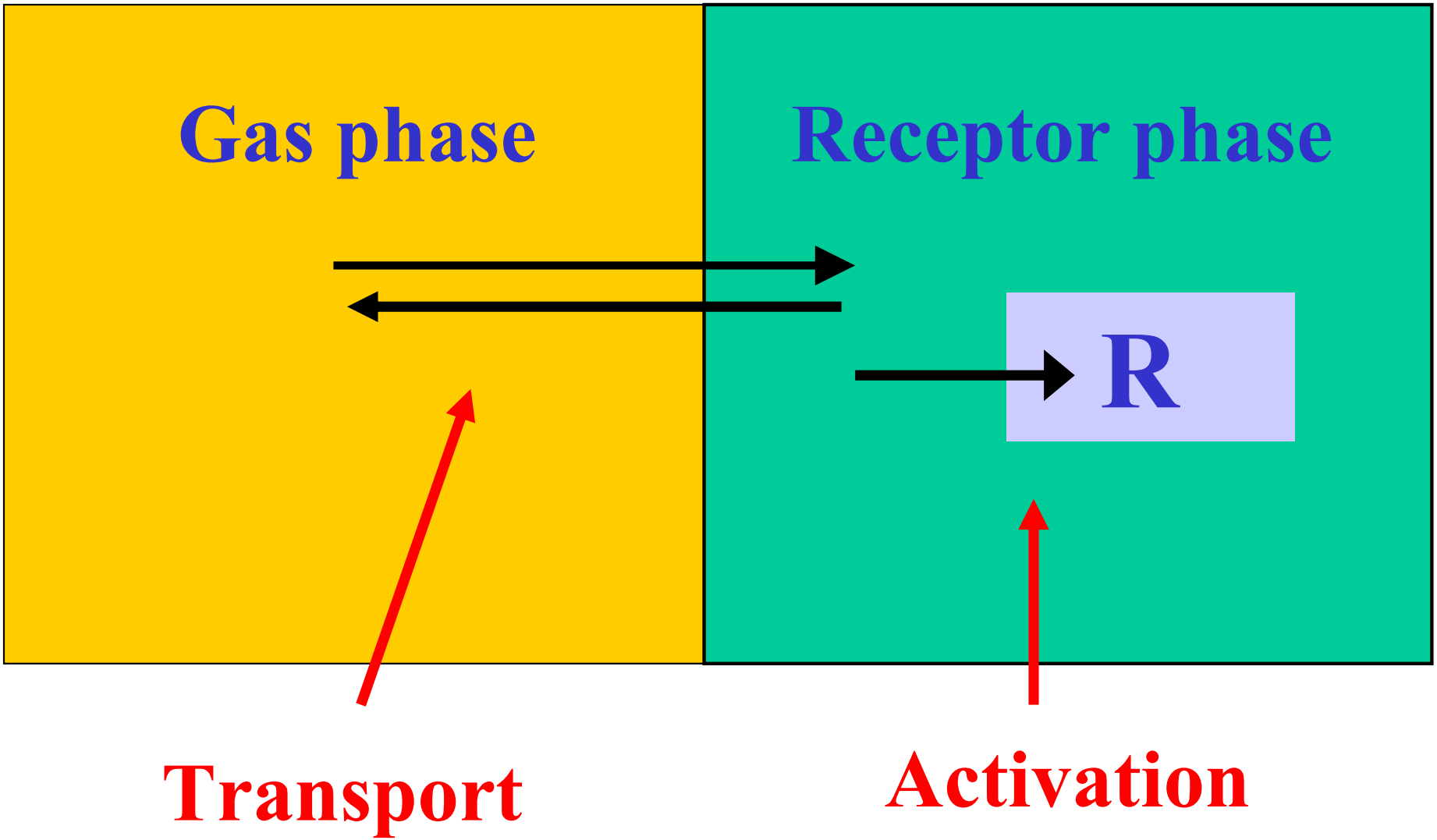
- **Tested** **200**
- **Found in tobacco smoke** **2000**
- **Industrial chemicals** **100,0000**

What Happens?

1. VOC in the air
2. VOC absorbed in the nose–concentrated
3. Activates a receptor
4. Brain interprets signals from receptor


Air
Odorant
Mucus layer
Receptor
Brain

A Two Stage Model



A Two-Stage Model

- **Stage 1. Transport (transfer) from gas to receptor area.**

  Structural effects are selective.
- **Stage 2. Interaction with receptor.**

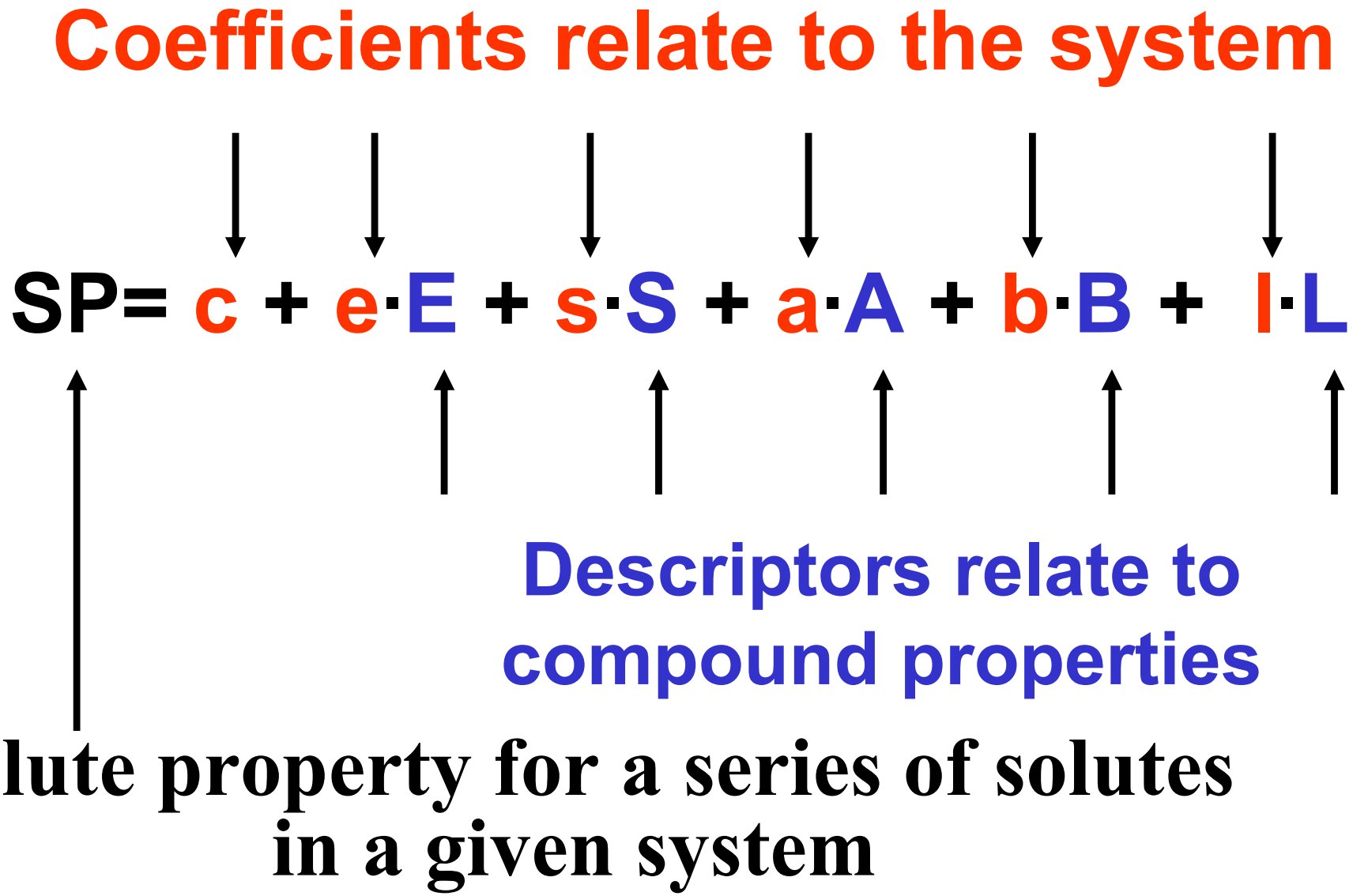
  Structural effects may be specific.

Transport can be modeled

General equation for rates of transfer or equilibrium from one phase to another phase.

Can be applied to first step

The General Equation



Descriptors

L Size – Log (gas-hexadecane)

E Dispersion - from ref index

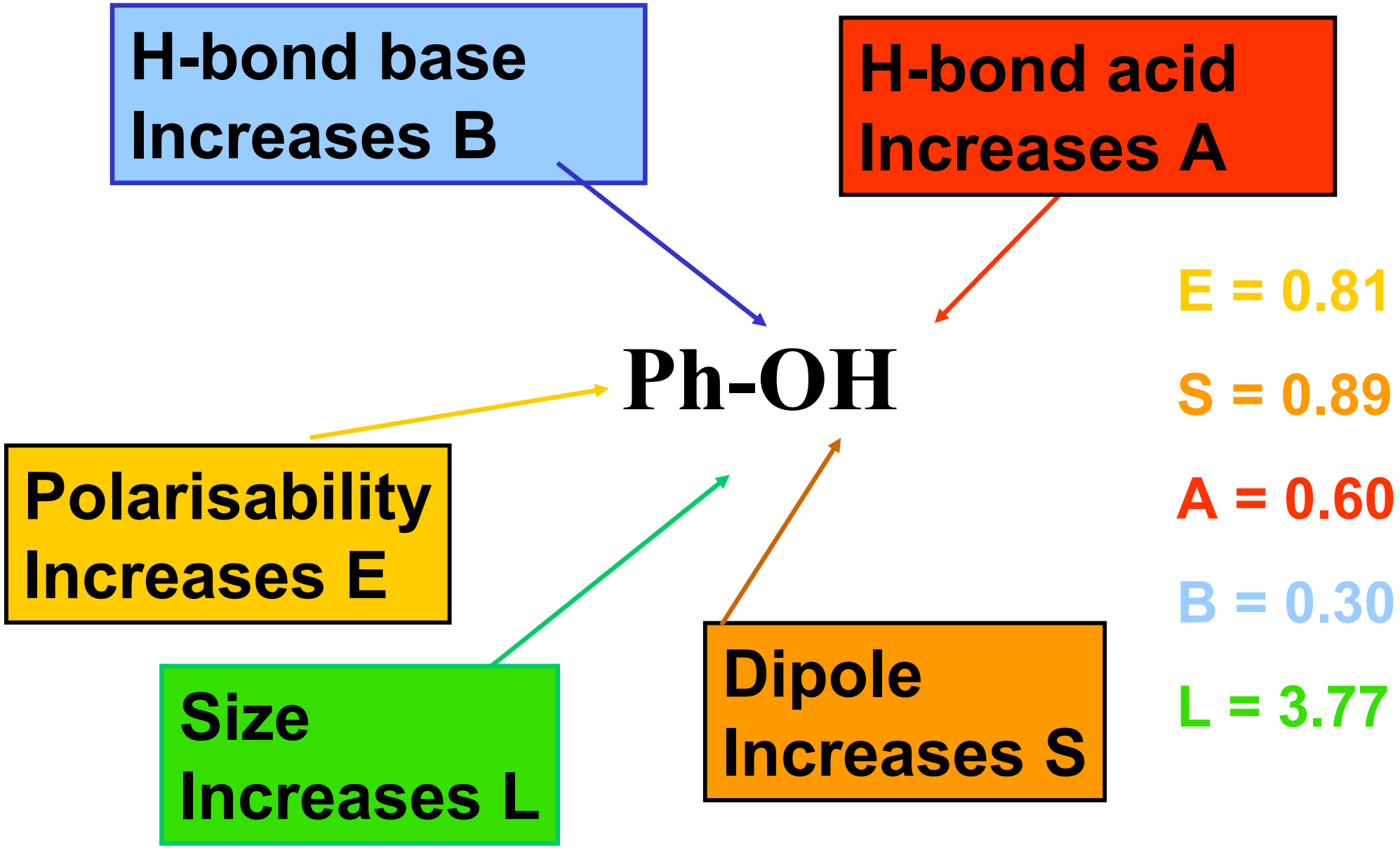
S Dipole and induced dipole

A H- bond acidity

B H- bond basicity

V McGowan Volume

Descriptors



(1) SP= c + e·E + s·S + a·A + b·B + l·L

(2) SP= c + e·E + s·S + a·A + b·B + v·V

(1) Gas to phase, (2) Phase to phase

Descriptors from GLC data

L = Gas-hexadecane partition constant at 25°C

Can obtain L by direct GLC on hexadecane

Descriptors from GLC data

$$I/10 = 6.67 + 8.92\,E + 20.00\,L$$

$$N = 138,\ R^2 = 0.999,\ SD = 0.45$$

GLC Retention Index on Squalane

Can calc L knowing I/10 and E

Descriptors from GLC data

$$I/10 = 2.99 - 22.68\,E + 52.86\,S + 21.69\,A + 20.58\,L$$

$N = 30$, $R^2 = 0.997$, $SD = 0.85$

GLC on Polar phase

Can calc S or A from I/10, E and L

Descriptor Calculations

Use a number of equations in V or L and solve for the unknown descriptors by ‘Solver’ in Excel

2-methylpentanoic acid

	Obs	Calc
Water-octanol (V)	1.95	1.92
Gas-water (V)	4.22	4.18
Gas-octanol (L)	6.15	6.10
Gas –water (L)	4.26	4.18
GLC cwax (L)	1.58	1.67
GLC ppe (L)	0.41	0.39
GLC tcep (L)	2.02	2.01
GCL zonyl (L)	0.86	0.87

SD = 0.053

E = 0.178

S = 0.59

A = 0.61

B = 0.45

L = 3.66

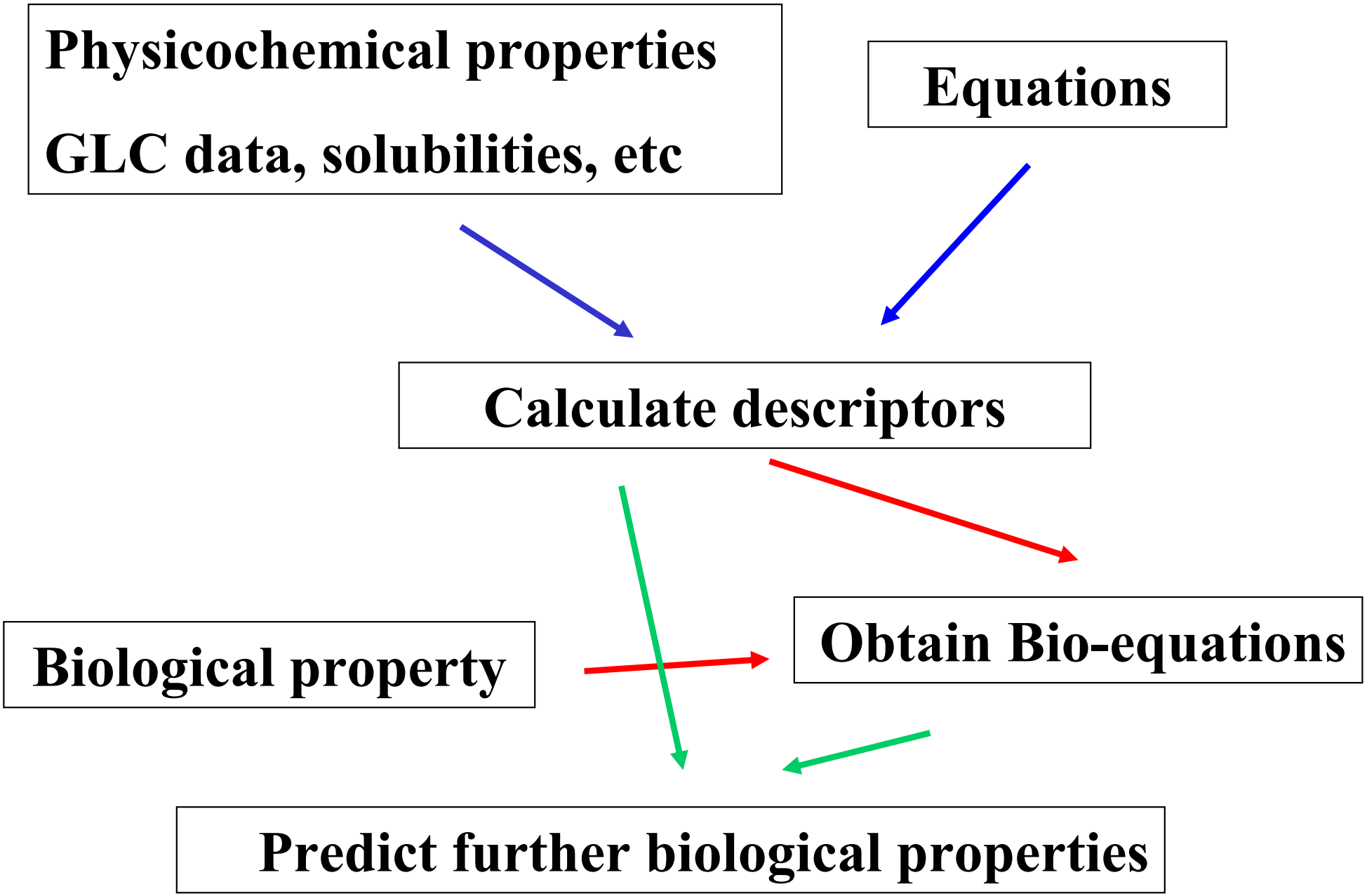
V = 1.028

Estratriol E = 1.97 V = 2.2575

Water to Solvent	Calc	Obs
Octanol	2.37	2.45
Benzene	-0.65	-0.69
Toluene	-0.86	-0.79
Ether	1.18	1.20
Isopropyl ether	1.08	0.90

S = 1.74 A = 1.06 B = 1.63

n = 5 sd = 0.11 log units


Physicochemical properties
GLC data, solubilities, etc
Equations
Calculate descriptors
Biological property
Obtain Bio-equations
Predict further biological properties

Gas to Methanol Partition

$$\mathbf{Log(K) = -0.00 - 0.22\,E + 1.17\,S + 3.70\,A + 1.43\,B + 0.769\,L}$$

$$\mathbf{n=93 \quad r^2 = 0.995 \quad sd = 0.13}$$

$$\mathbf{K = C(MeOH) / C(Gas)}$$

Gas to Brain Partition

$$\mathrm{Log(K)} = -0.97 - 0.36\,E + 0.66\,S + 3.56\,A + 1.60\,B + 0.636\,L$$

$$n=81 \quad r^2 = 0.923 \quad sd = 0.35$$

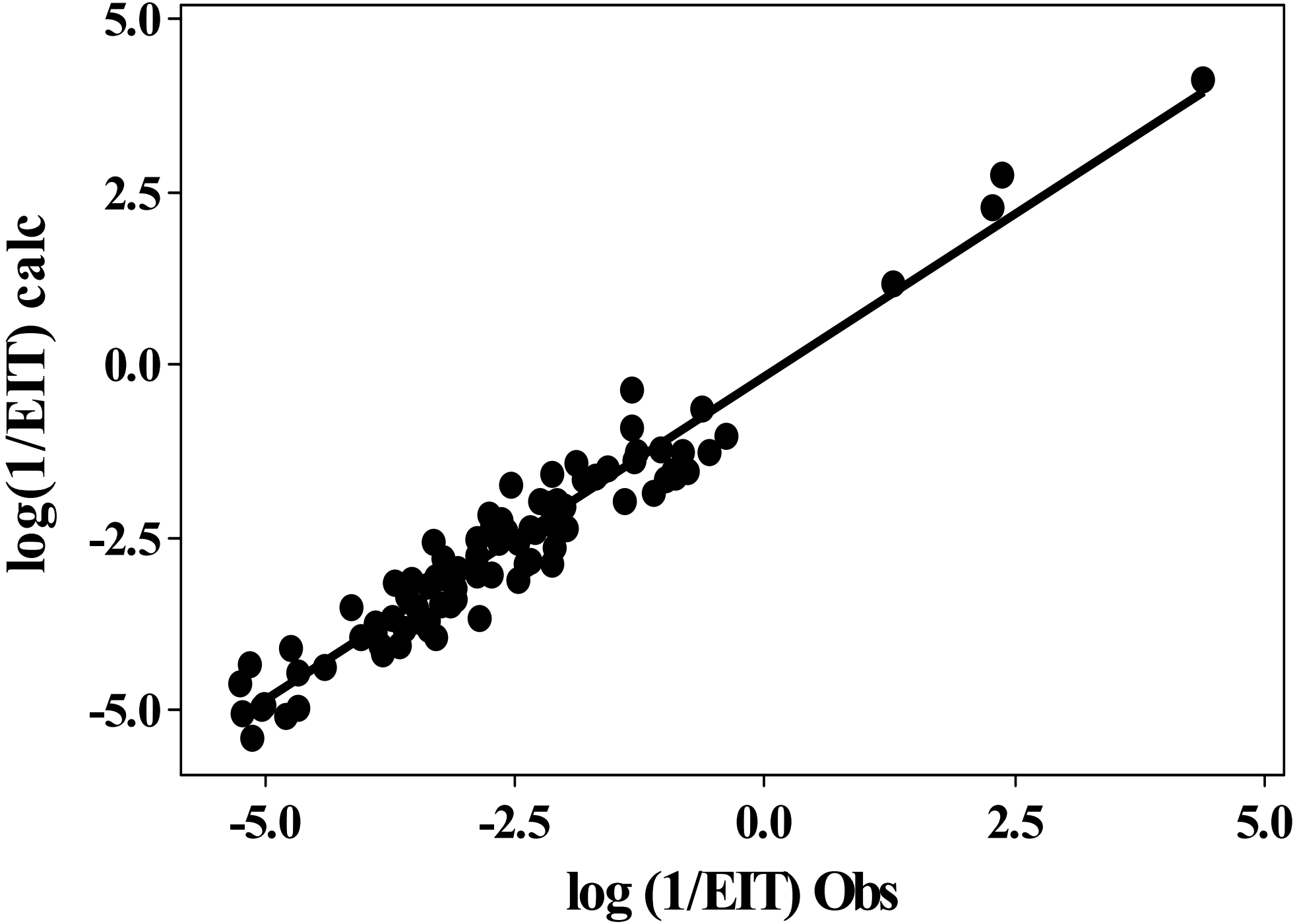
$$K = C(\mathrm{Brain}) / C(\mathrm{Gas})$$

Eye irritation

Log (1/EIT) = -7.89 – 0.38 E + 1.87S + 3.78A + 1.17B + 0.78L + 0.57 Idr

N = 54, R^2 = 0.936, SD = 0.43

Simple transport accounts for 94%

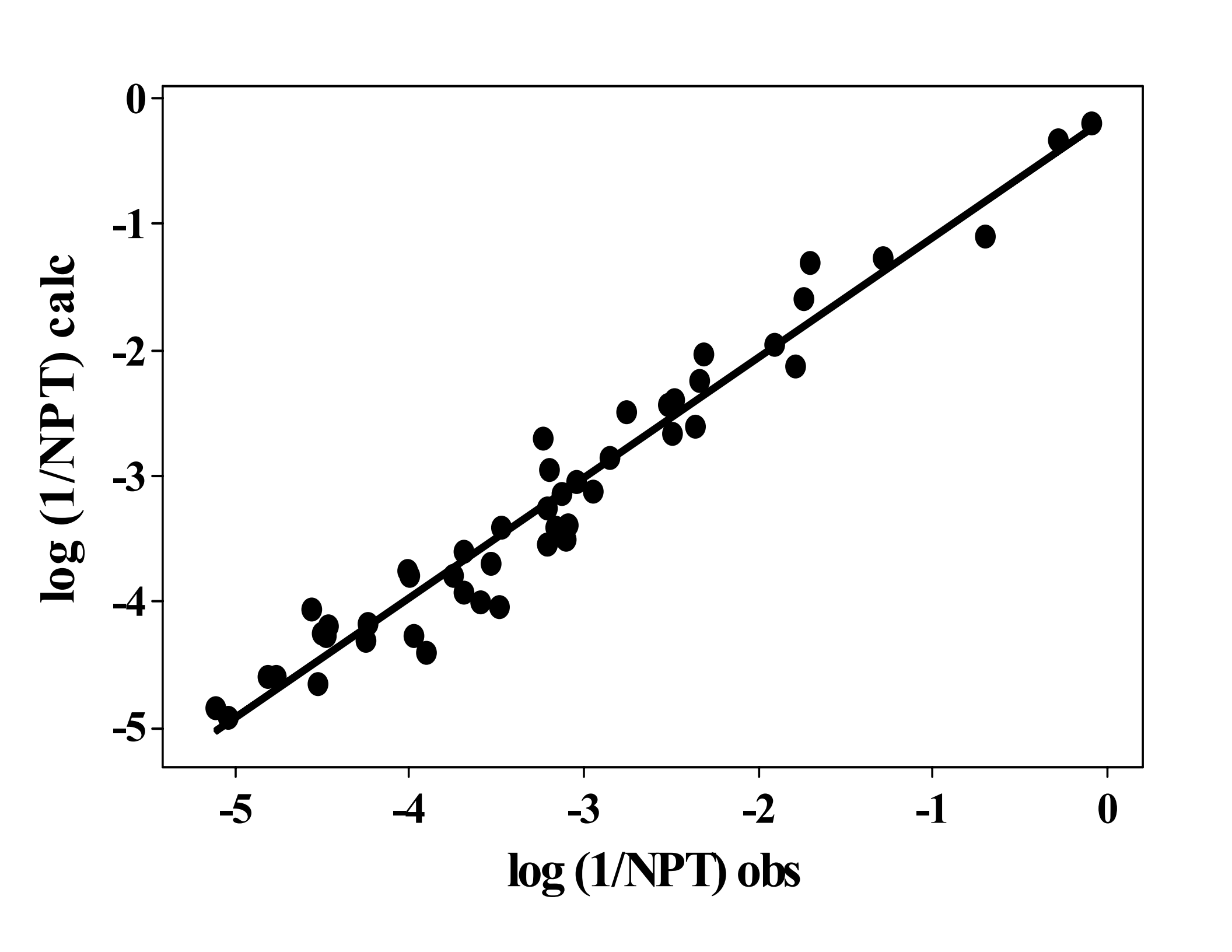

5.0
2.5
0.0
-2.5
-5.0
log(1/EIT) calc
-5.0
-2.5
0.0
2.5
5.0
log (1/EIT) Obs

Nasal Pungency

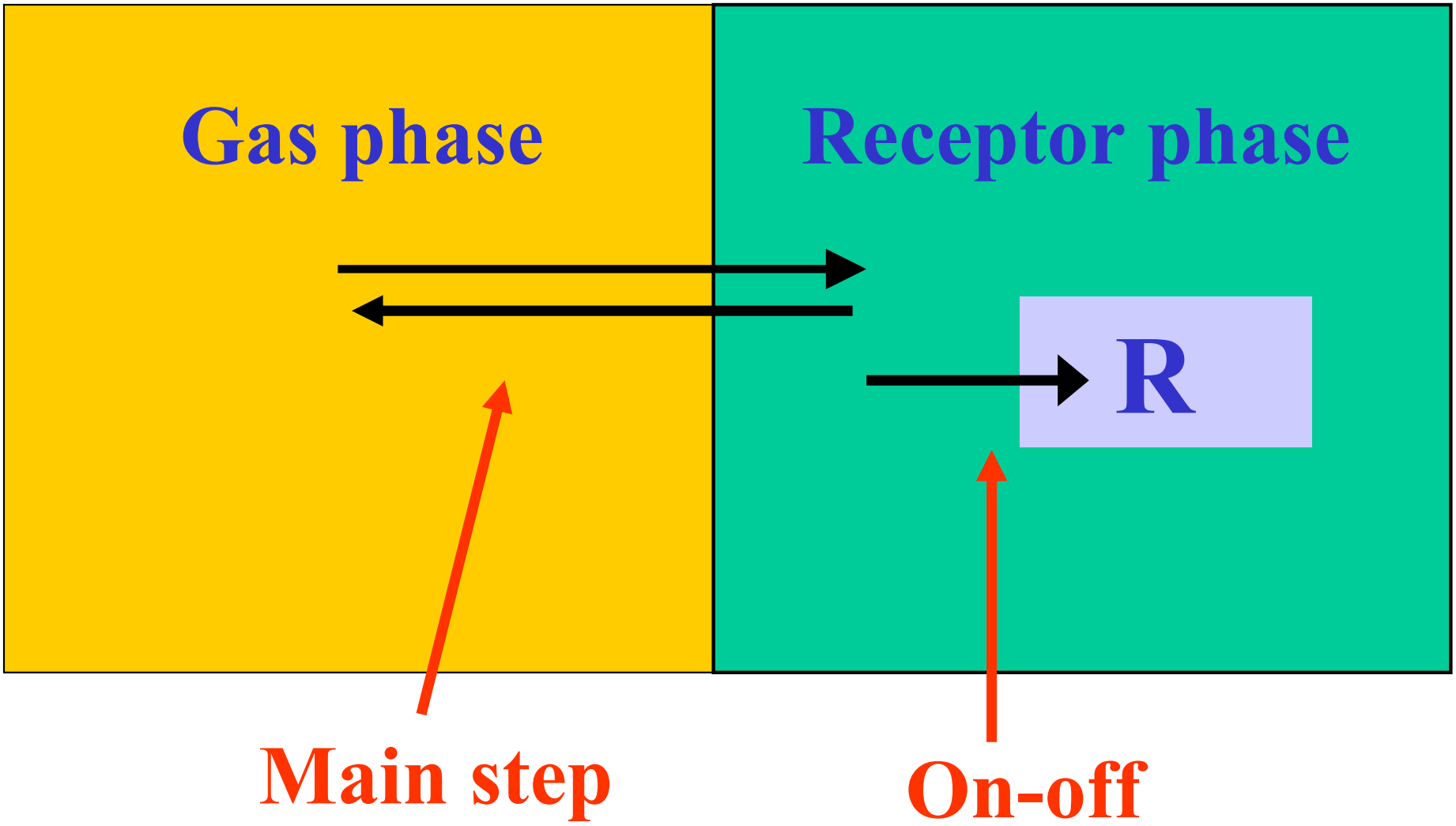
$$\text{Log } (1/NPT) = -8.22 + 1.69S + 3.35A + 1.10B + 0.90L$$

$$N = 49,\ R^2 = 0.951,\ SD = 0.27$$

Simple transport accounts for 95%


0
-1
-2
-3
-4
-5
log (1/NPT) calc
-5
-4
-3
-2
-1
0
log (1/NPT) obs

A Two Stage Model



Odor Thresholds

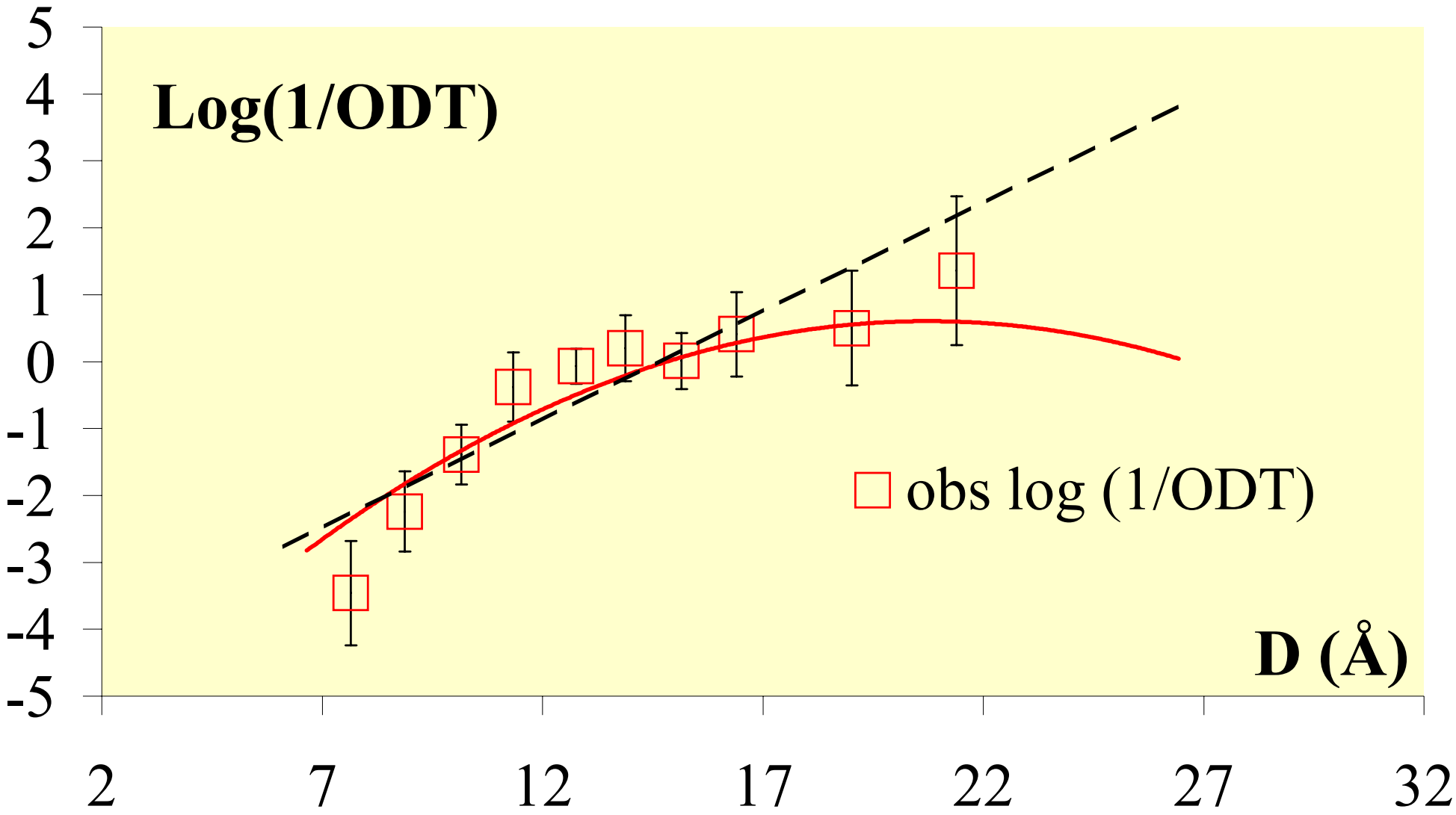
$$\text{Log } (1/\text{ODT}) = -5.22 + 0.70E + 1.87S + 0.66A + 1.75B + 0.70L$$

$$N = 51,\ R^2 = 0.813,\ SD = 0.53$$

13 Compounds excluded: acids, aldehydes

Simple transport accounts for only 81%

Obs log (1/ODT) values against the VOC maximum length D for the homologous series of acetates



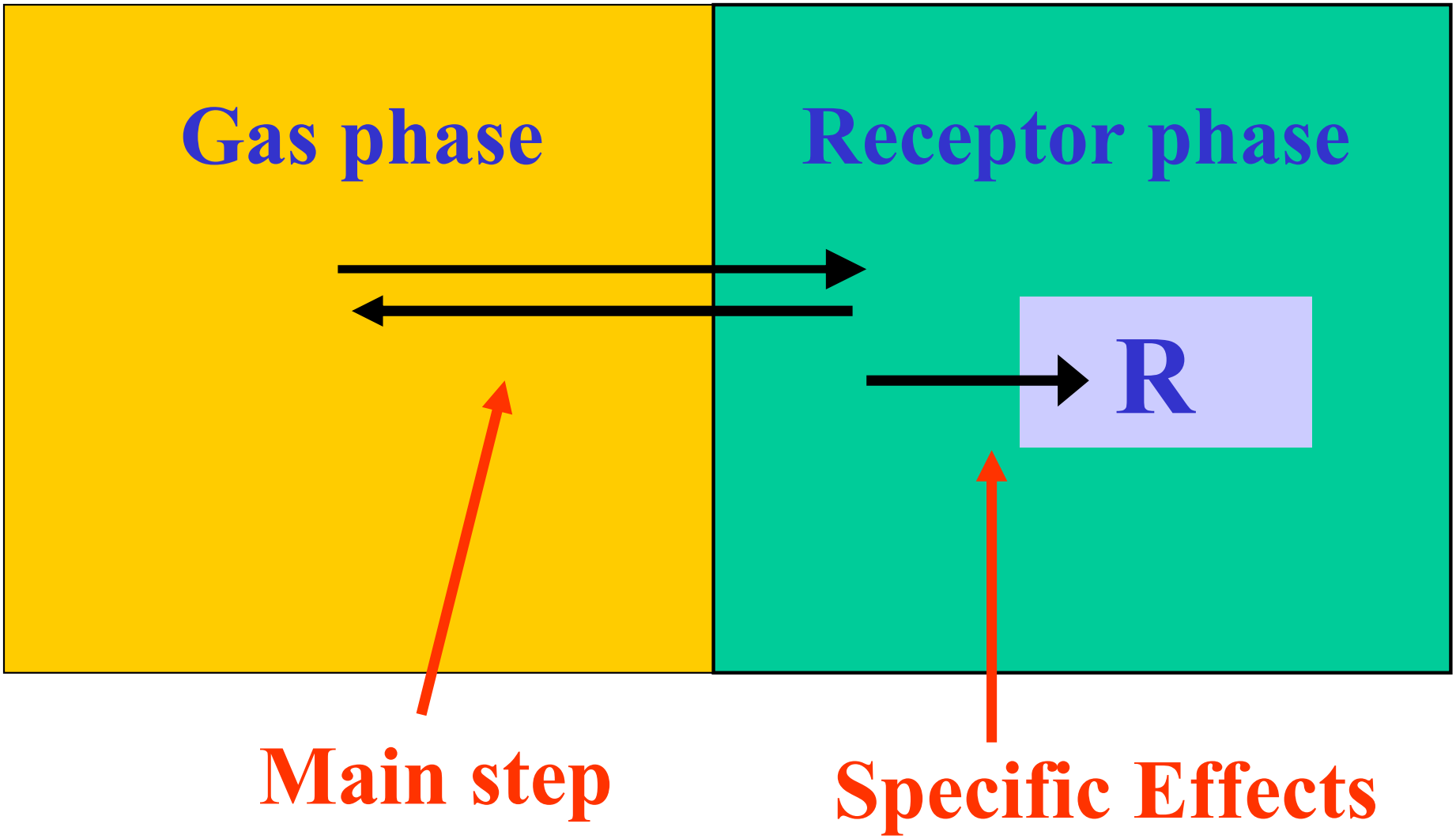
Odor Thresholds

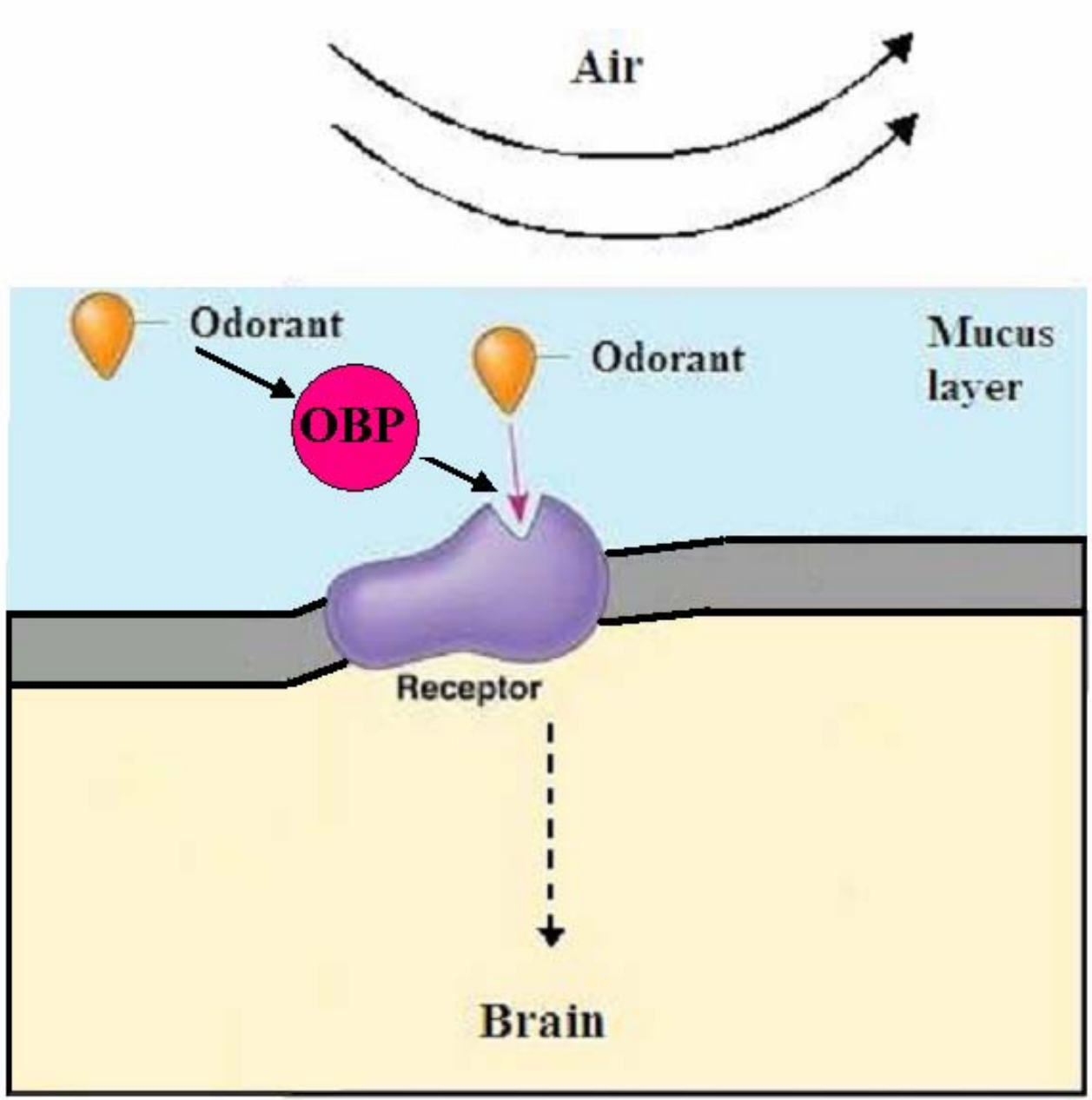
$$\text{Log } (1/\text{ODT}) = -6.85 + 0.38E + 2.14S + 1.42A + 1.43B + 1.57L - 0.104L^2$$

$$N = 51,\ R^2 = 0.850,\ SD = 0.47$$

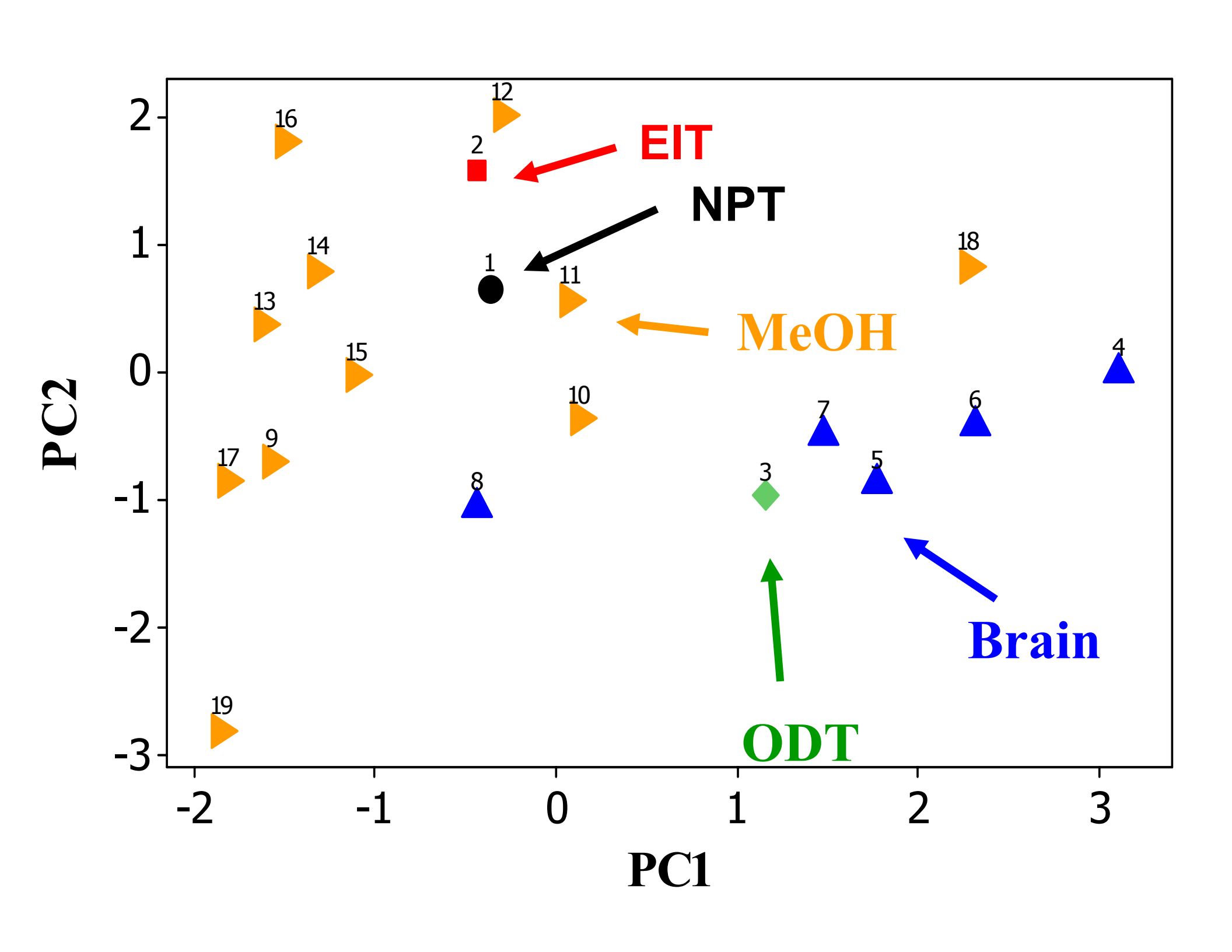
Include parabolic term in L and L^2

A Two Stage Model




Air
Odorant
OBP
Odorant
Mucus layer
Receptor
Brain

Phase	e	s	a	b	l
NPT	0.00	1.69	3.35	1.10	0.90
EIT	-0.38	1.87	3.78	1.17	0.78
ODT	0.70	1.87	0.66	1.75	0.70
Brain	0.26	0.41	3.36	2.03	0.59
Fat	0.05	0.73	1.78	0.33	0.74
MeOH	-0.22	1.17	3.70	1.43	0.77
NMF	-0.26	2.00	4.56	0.43	0.71

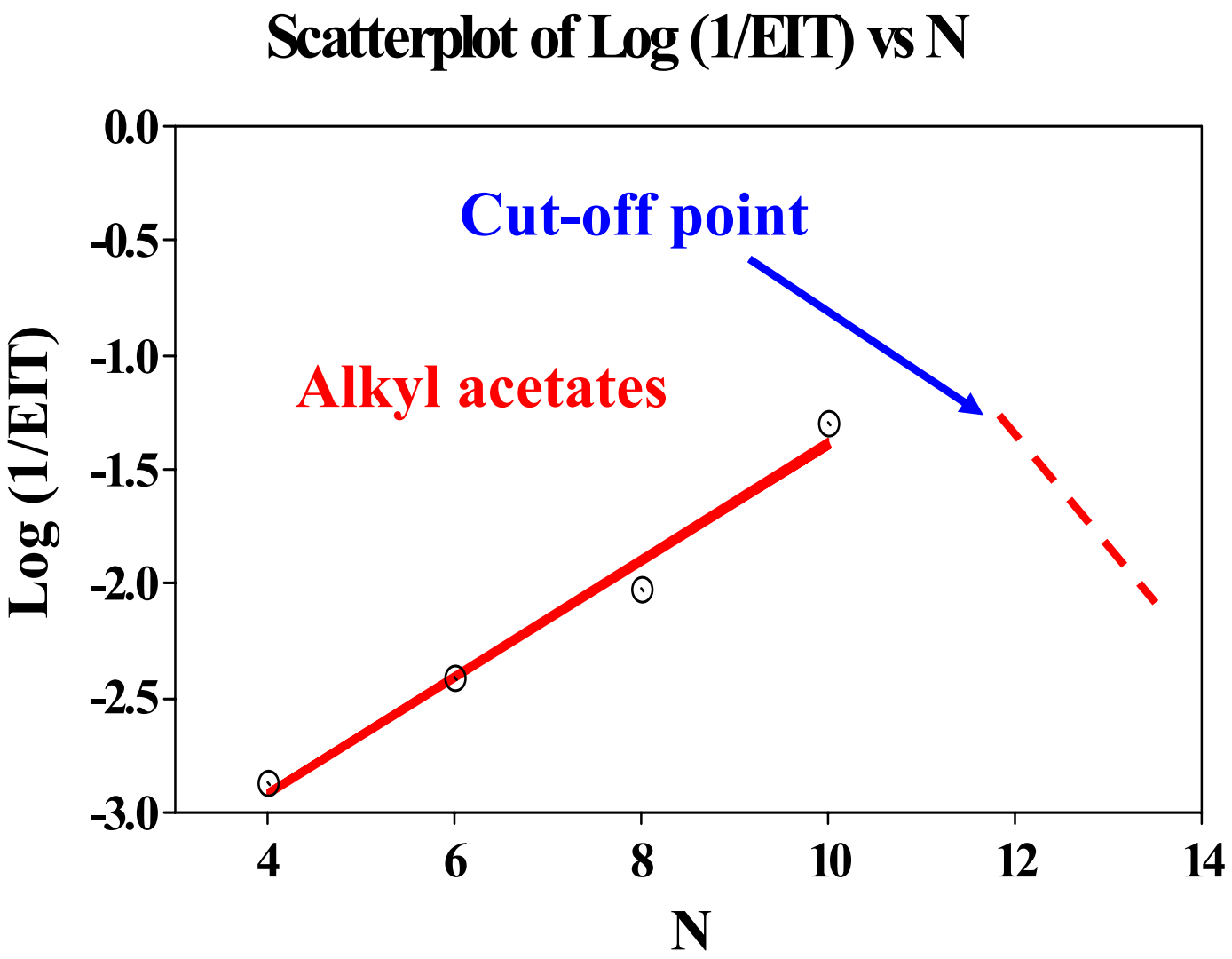

EIT
NPT
MeOH
Brain
ODT
PC1
PC2
-2
-1
0
1
2
3
-3
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19

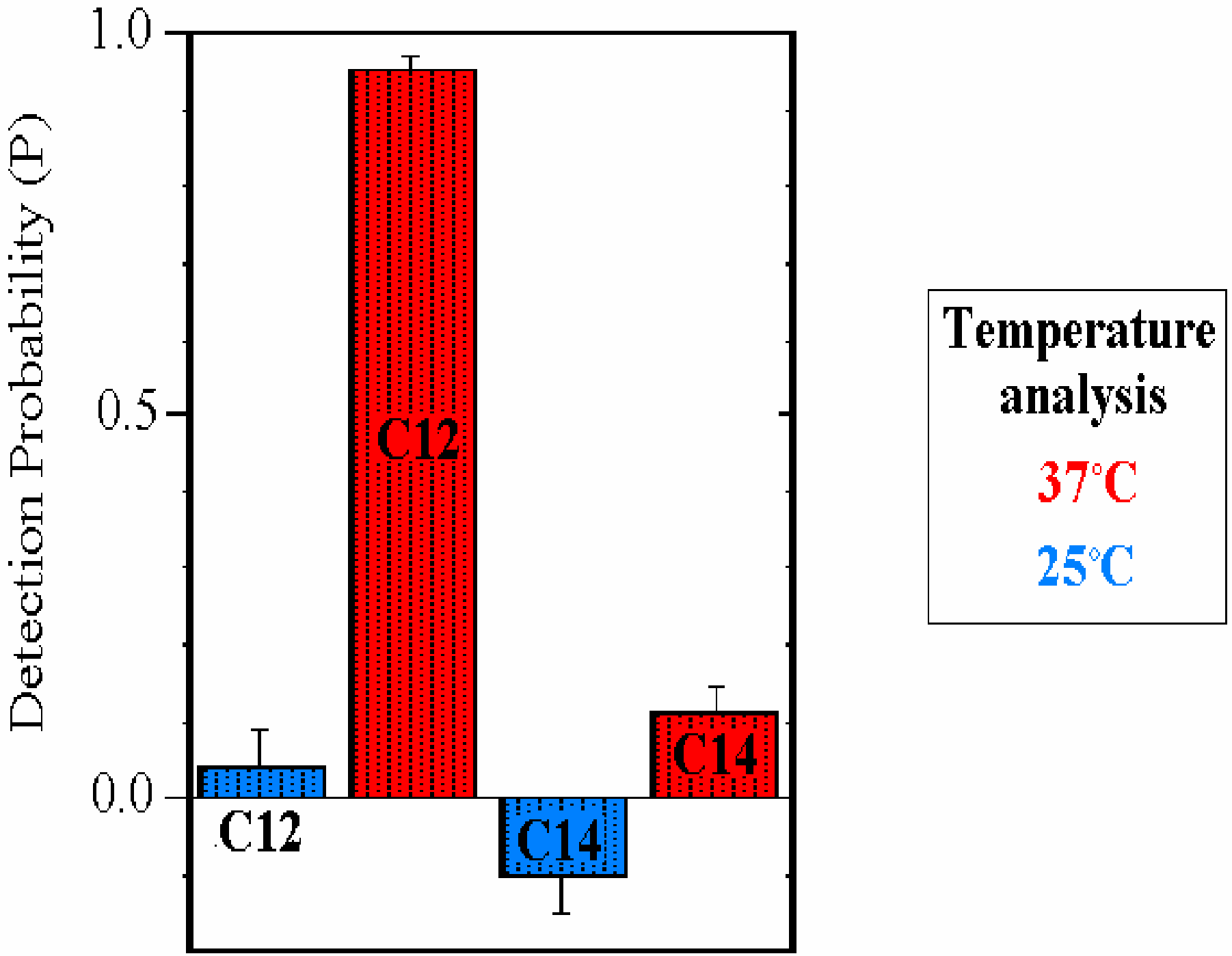
Prediction of Thresholds

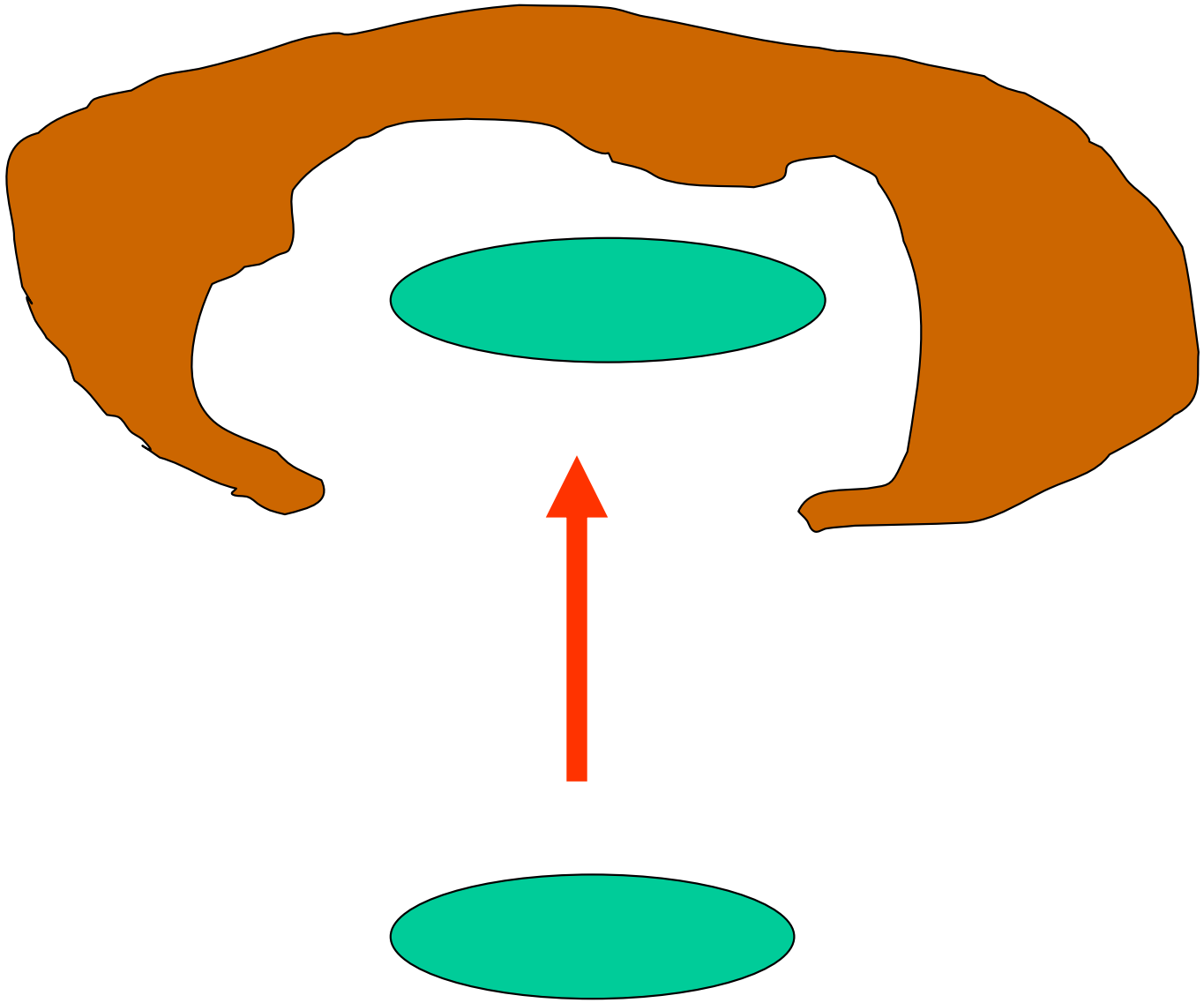
VOC	NPT	ODT
CF2Cl2	-7.0	-5.3
2-Methylhexane	-5.5	-3.1
Octane	-4.9	-2.5
2-Butanone	-4.4	-1.7
a-Pinene	-3.9	-1.4
2-Butoxyethanol	-2.0	0.5
Phenol	-1.0	1.5
Hexadecanoic acid	3.2	4.9

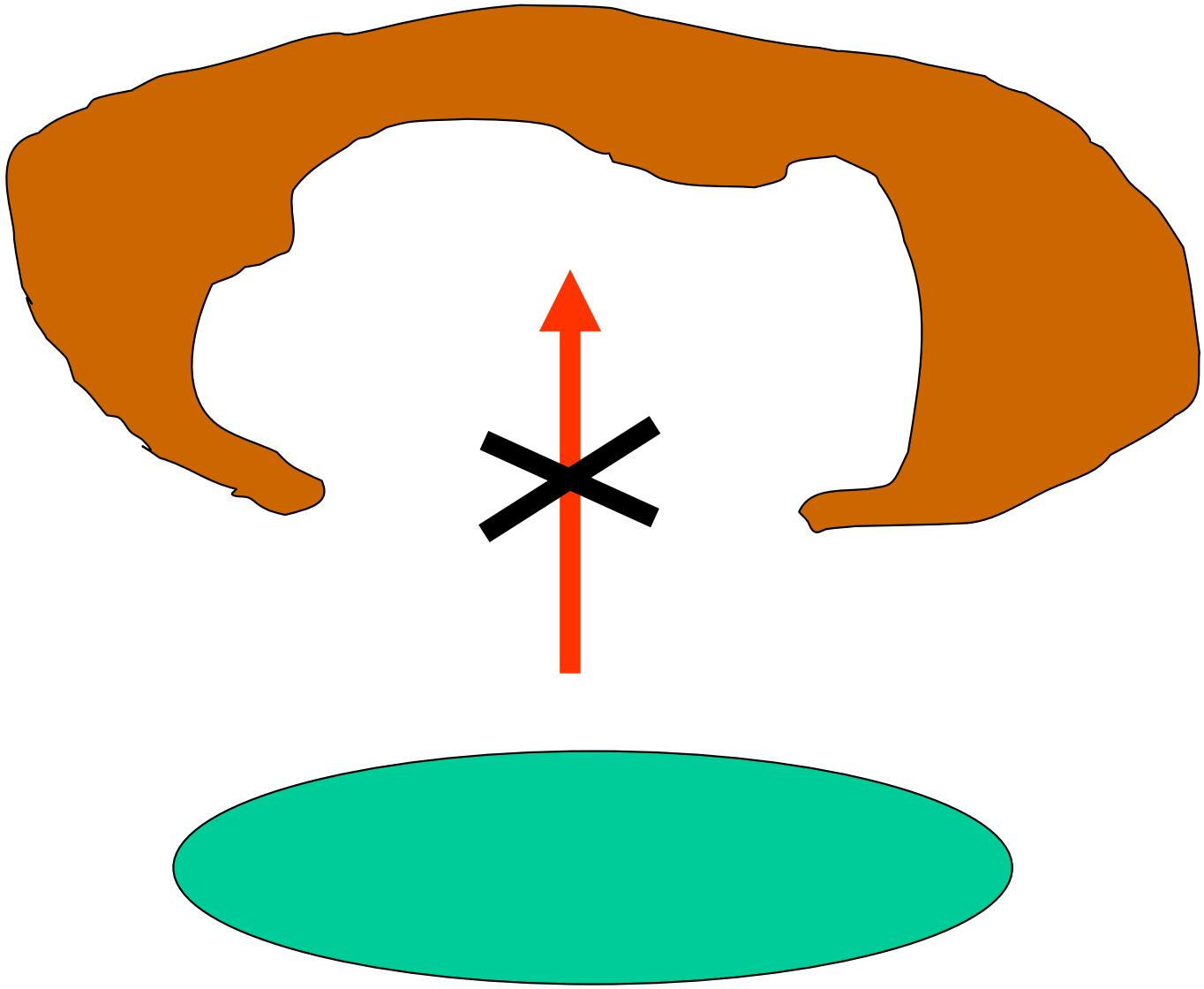
VOC Thresholds

- **Can predict effects on humans**
- **Can predict order of potency**


Scatterplot of Log (1/EIT) vs N
Cut-off point
Alkyl acetates
Log (1/EIT)
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
4
6
8
10
12
14
N


1.0
0.5
0.0
Detection Probability (P)
C12
C14
C12
C14
Temperature analysis
37°C
25°C

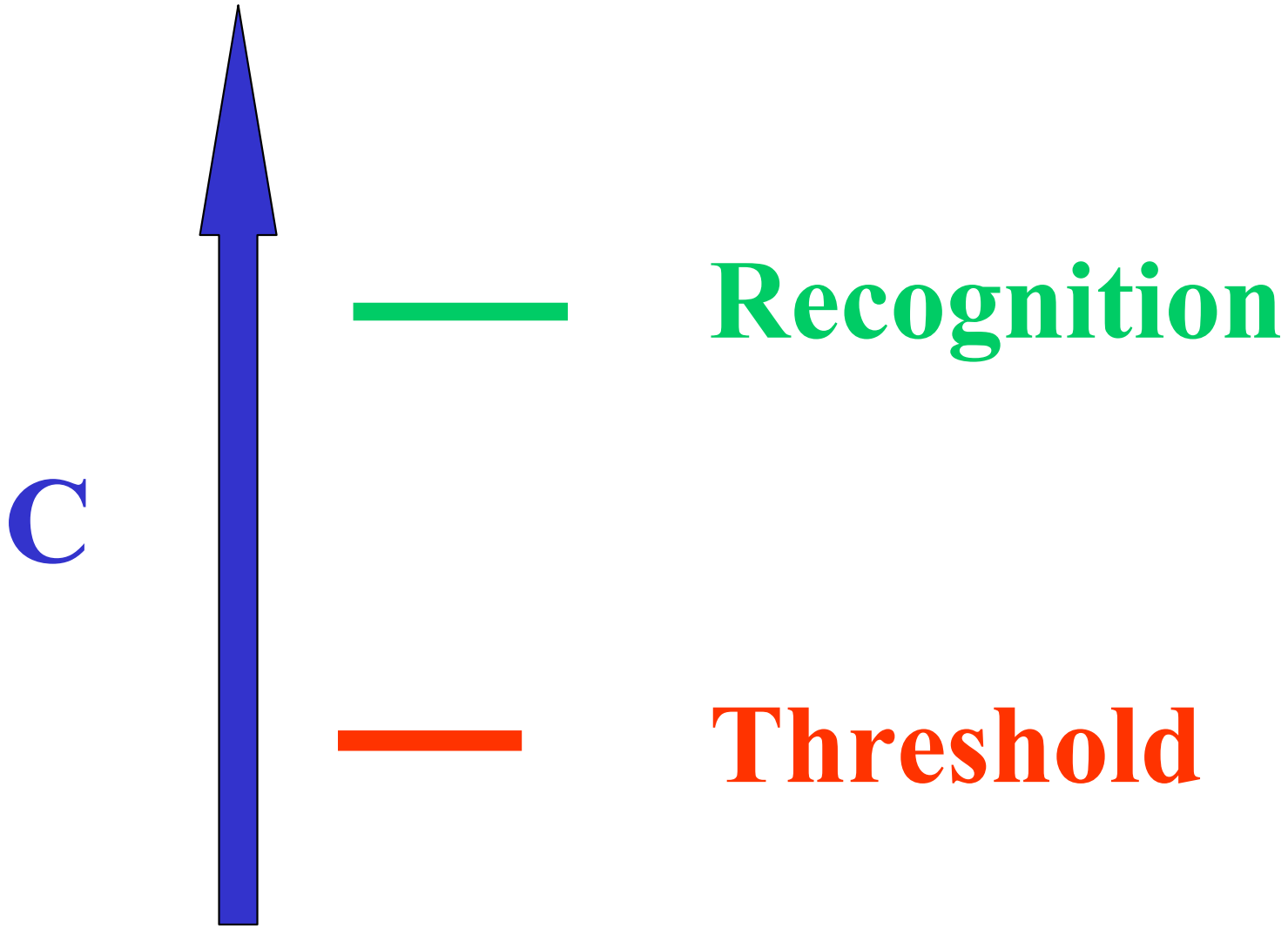




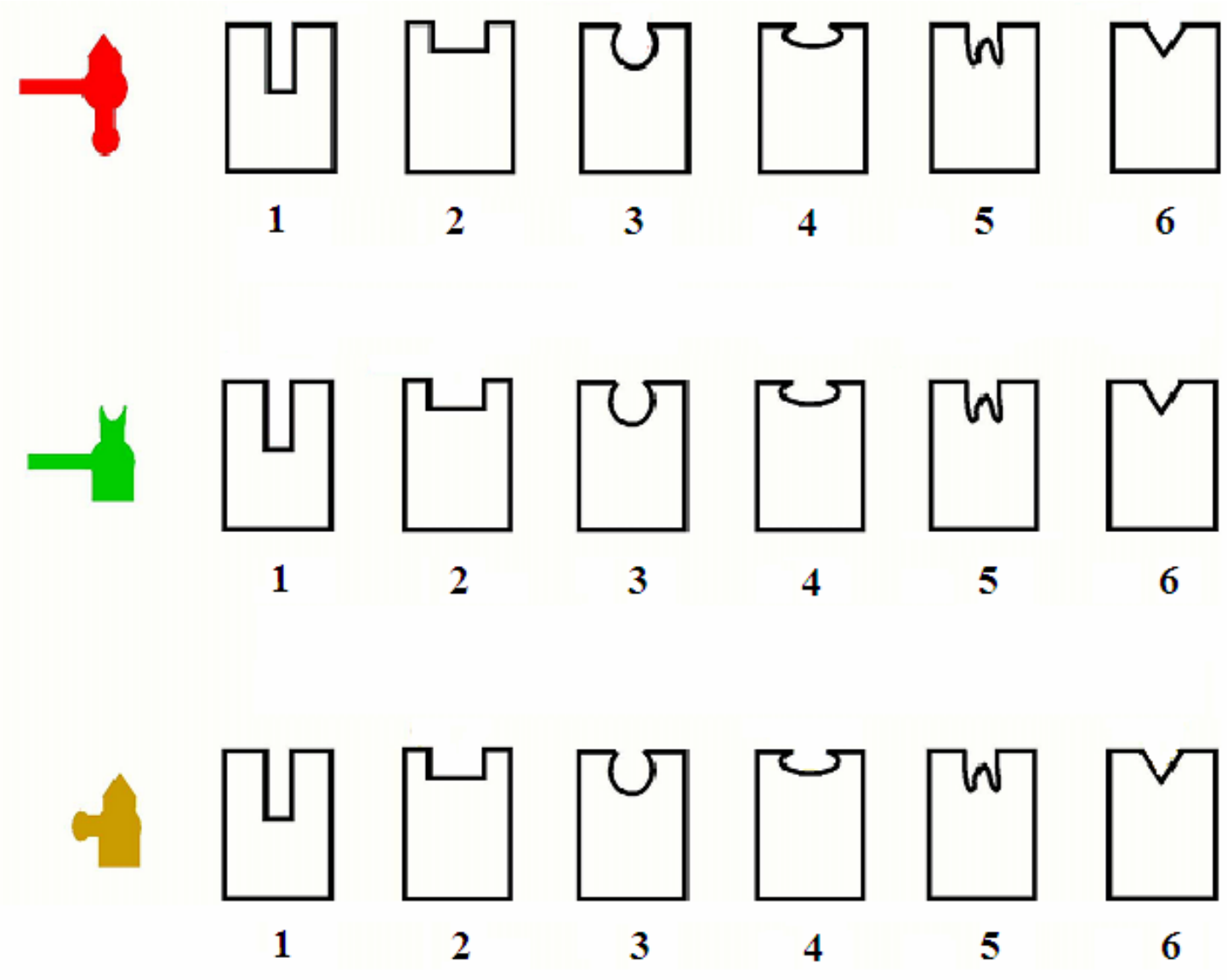
Inhalation Anesthetics

$$\text{Log } (1/P) = -0.75 - 0.03\ E + 1.56\ S + 3.59\ A + 1.41\ B + 0.69\ L$$

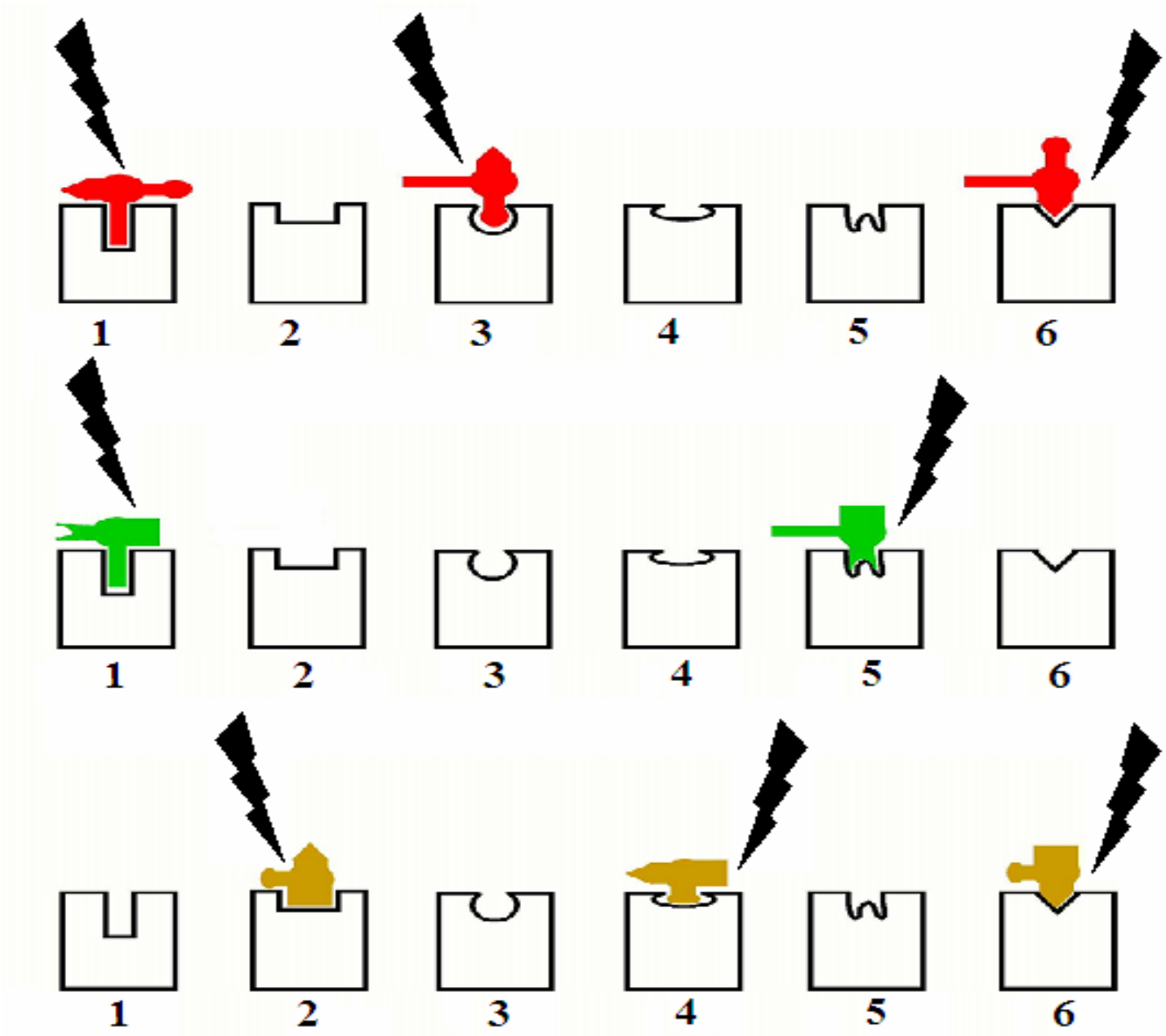
$$N = 148,\ SD = 0.19,\ R^2 = 0.985,\ F = 1856.1$$


C
Recognition
Threshold

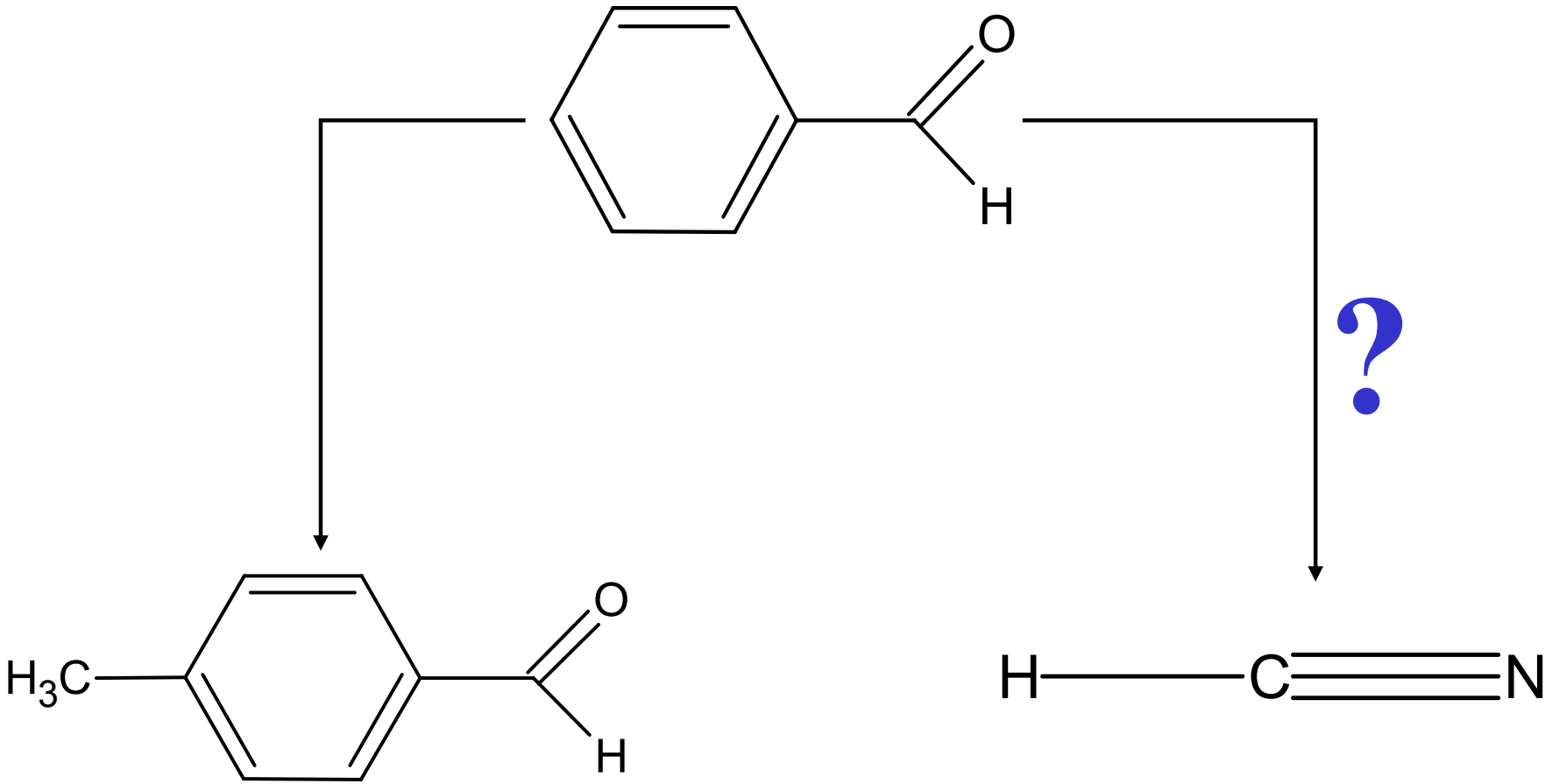
Odor Recognition



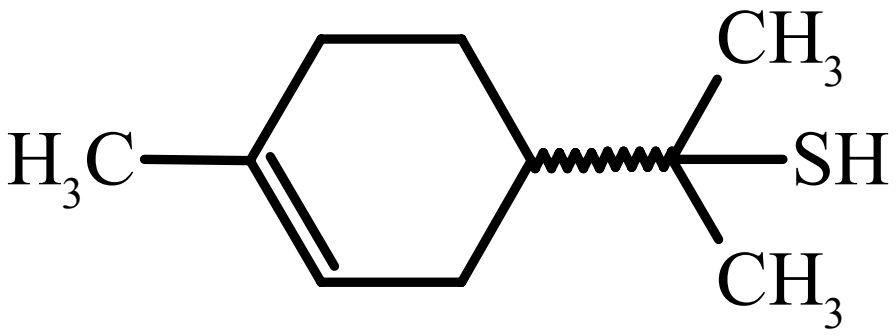
Electrical signal



The case of benzaldehyde



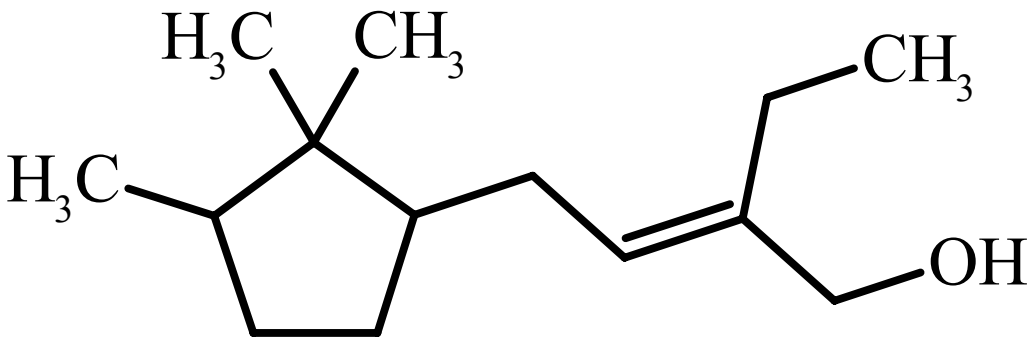
The case of 1-p-menthen-8-thiol



Low level : grape fruit

High level : very obnoxious smell

The case of bangalol



bangalol

Musk **Sandalwood**

William Cain

Enrique Cometto-Muniz

Ricardo Sanchez

Javi Gil-Lostes

NIH -USA