INTEGRATED INSILICO SCREENING AND DRUG DESIGN SYSTEM

ACTIVITY, ADME, TOXICITY, PROPERTY ANALYSIS AND PREDICTION

Kohtaro Yuta[1], Jose Martin Ciloy [2], Masato Kitajima[2], Wojtek Plonka[3] and Munetaka Sawada[1]

1.Fujitsu Ltd., 2.Fujitsu Kyushu System Engineering Ltd., 3. FQS Poland Sp. z o.o.

FUJITSU

THE POSSIBILITIES ARE INFINITE

1 *"Integrated" concept*

2 *Application pattern of integrated concept*
"Integrated in silico screening"
"Integrated in silico drug design"

3 *Multivariate and pattern recognition*
pattern analysis and scientific analysis

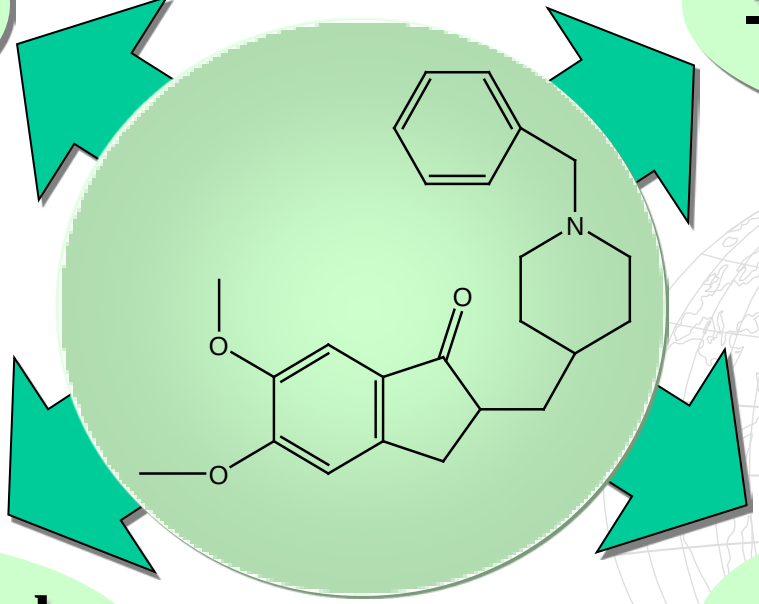
4 *System overview*
ADMEWORKS:Prediction system
ModelBuilder:Chemical data analysis system

5 *Predictive models*

Drug properties and compound structure

ADME properties

Pharmacological activity



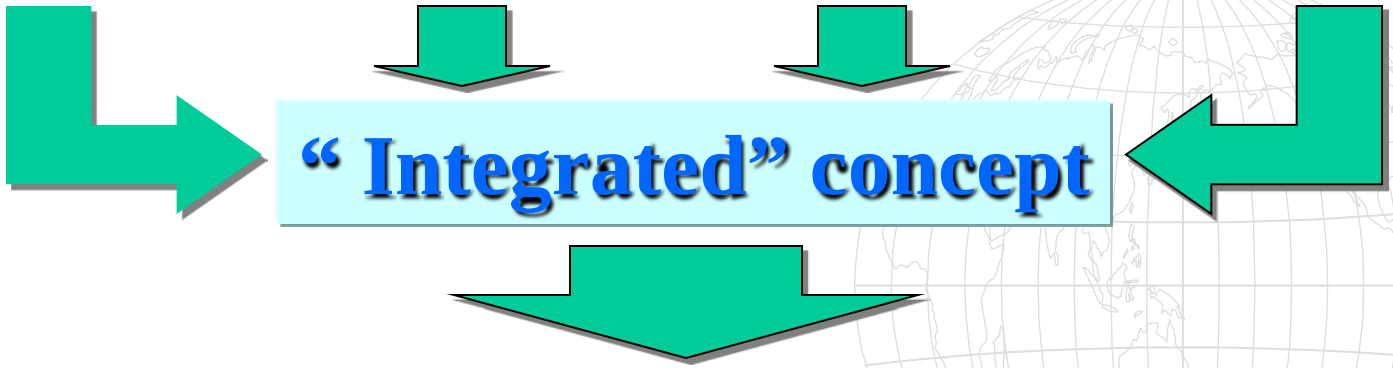
Physico chemical properties

Toxicity

"Integrated" concept for drug development

Activity + ADME + Toxicity + Property

All drug properties shall be considered at the same time



" Integrated" in silico screening & drug design

1 *"Integrated" concept*

2 *Application pattern of integrated concept*
"Integrated in silico screening"
"Integrated in silico drug design"

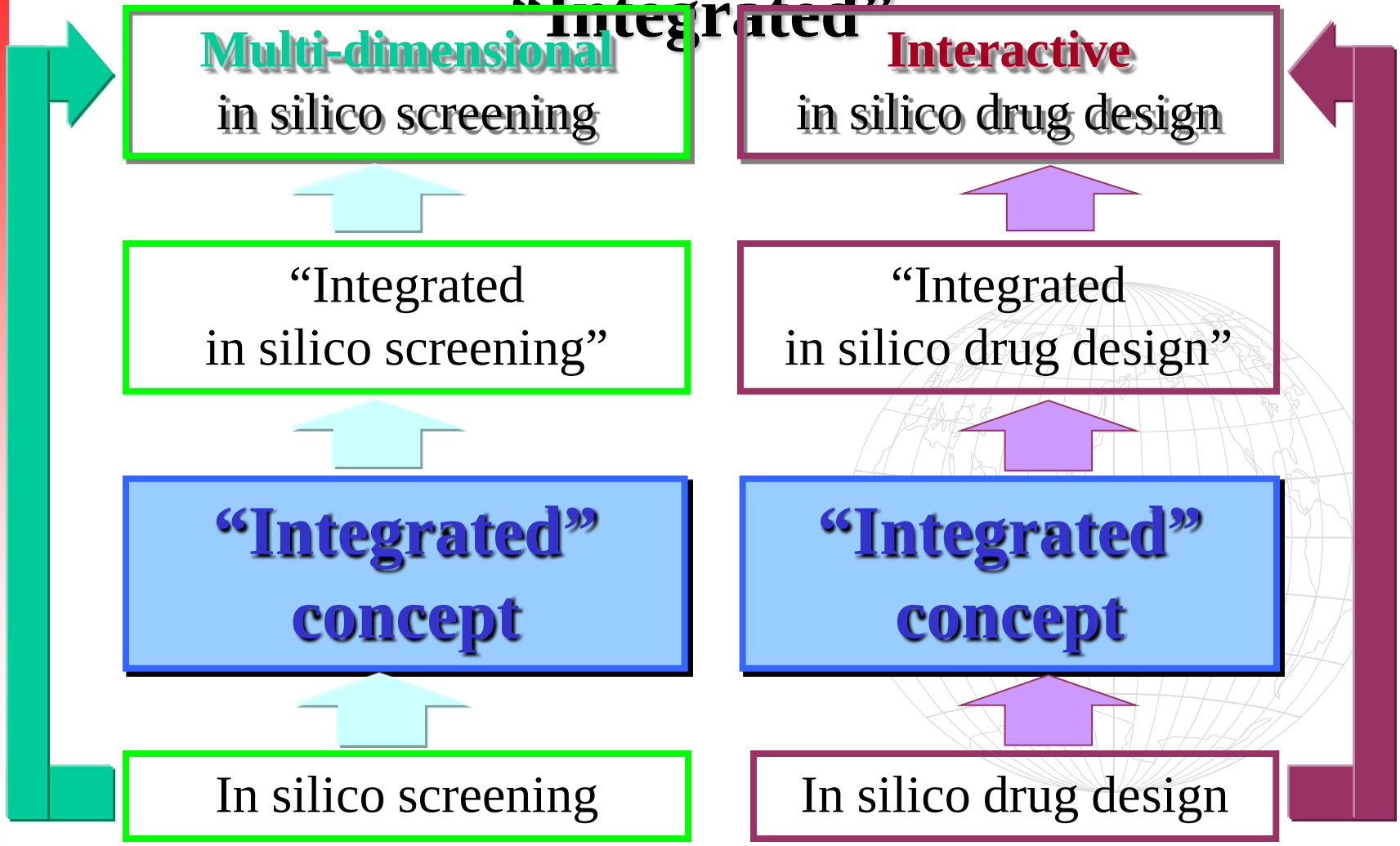
3 *Multivariate and pattern recognition*
pattern analysis and scientific analysis

4 *System overview*
ADMEWORKS:Prediction system
ModelBuilder:Chemical data analysis system

5 *Predictive models*

Application pattern of integrated concept

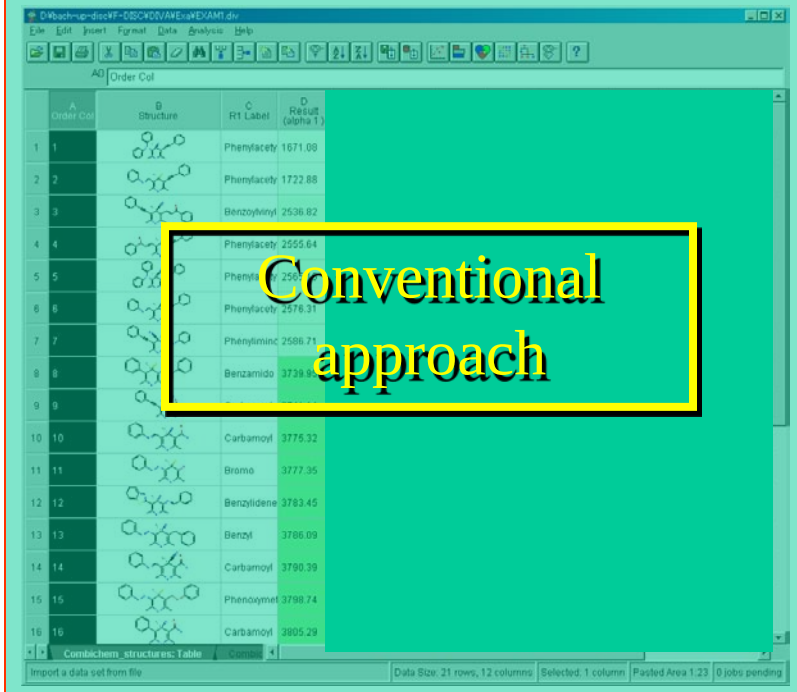
Two application style of "Integrated"



"Integrated" in silico screening

One-dimensional screening

one activity／compound



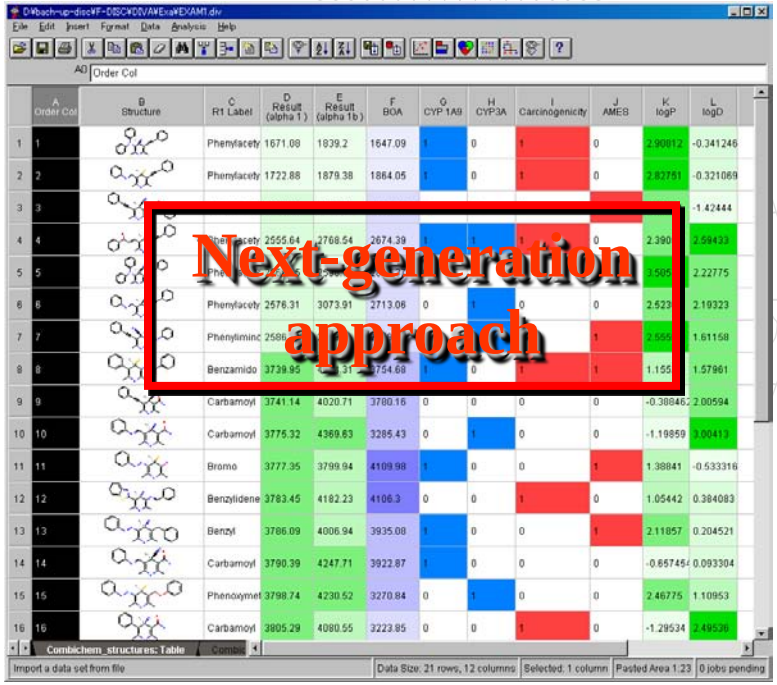
Conventional approach

Multi-dimensional screening

multiple activities

- **" ADME**
- **" toxicities**
- **" properties**

／ compound

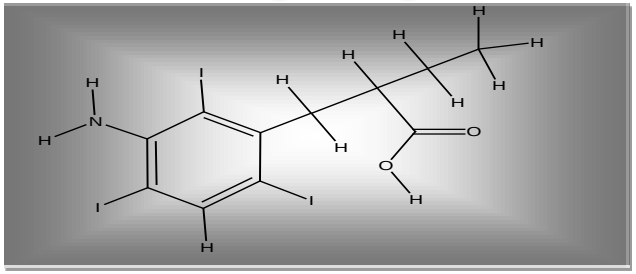


Next-generation approach

"Interactive and real-time" drug design

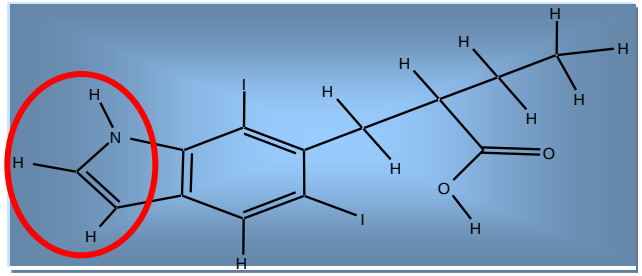
* **Check the effects of structure modifications on compound properties real-time**

Starting compound



modification

activity
ADME
toxicity
property



Modified compound

antibacterial	Anti-inflammatory	anticancer	・・・・・	pesticide
carcinogenicity	Ames test	LD50	・・・・・	others

ADME and properties

Caco－2	BBB	CYP
LogP	pKa	$LogD_{7.4}$

antibacterial	Anti-inflammatory	anticancer	・・・・・	pesticide
carcinogenicity	Ames test	LD50	・・・・・	others

Information on different properties of different compounds is available anytime

1 *"Integrated" concept*

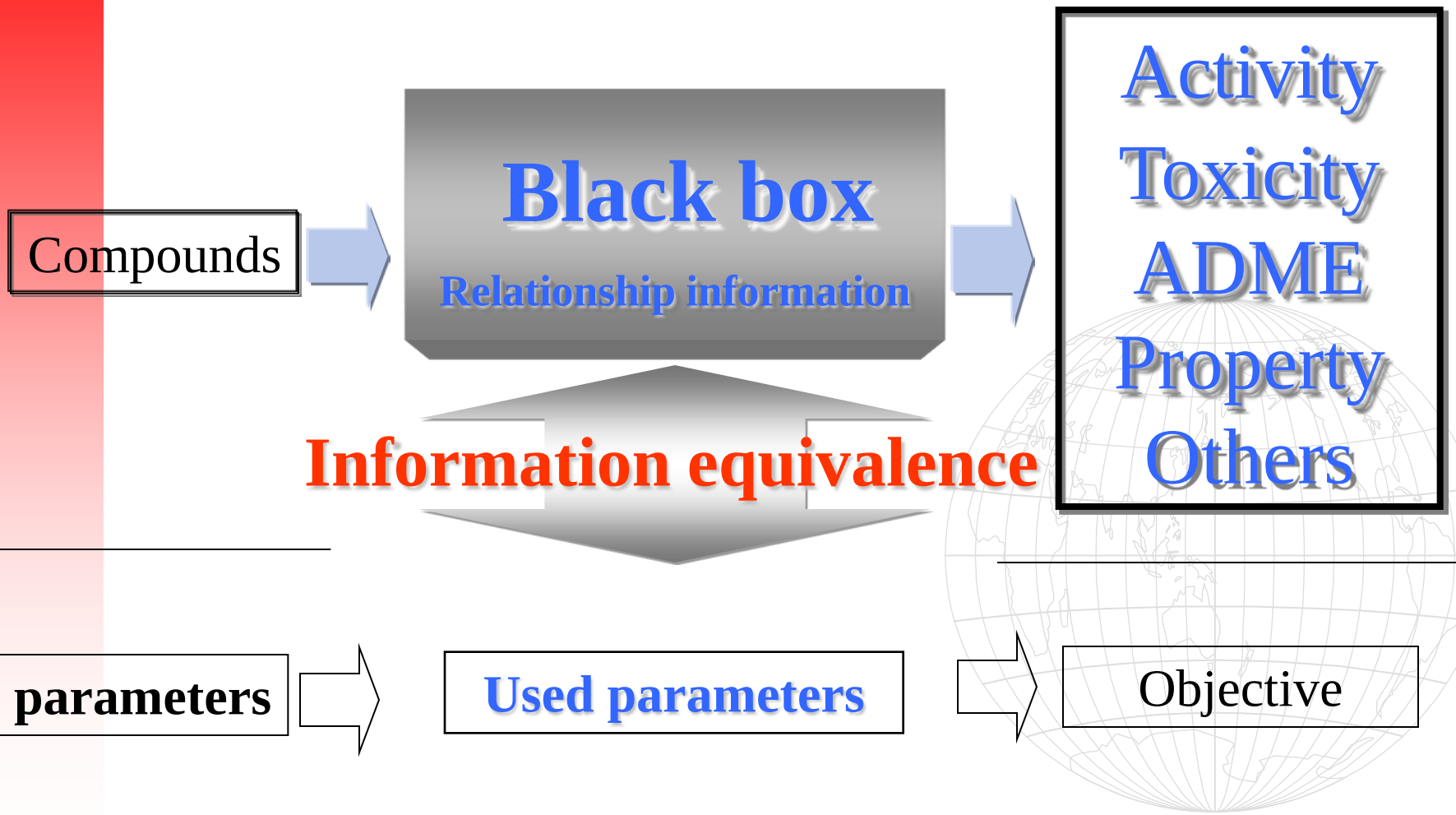
2 *Application pattern of integrated concept*
"Integrated in silico screening"
"Integrated in silico drug design"

3 *Multivariate and pattern recognition*
pattern analysis and scientific analysis

4 *System overview*
ADMEWORKS:Prediction system
ModelBuilder:Chemical data analysis system

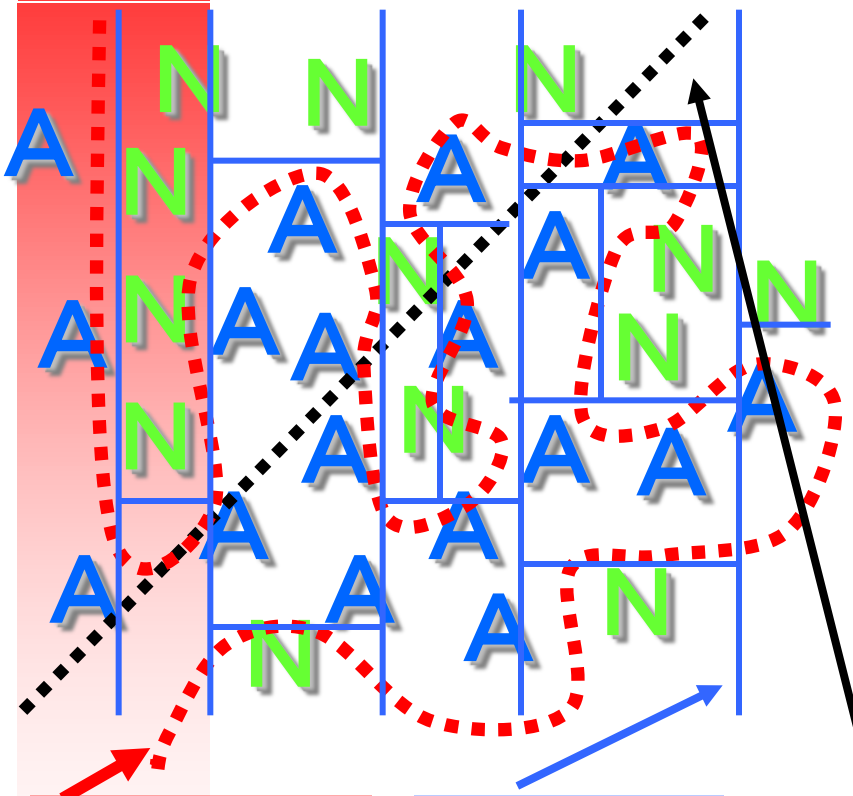
5 *Predictive models*

Basic priniciple of data analysis by MVA & PR



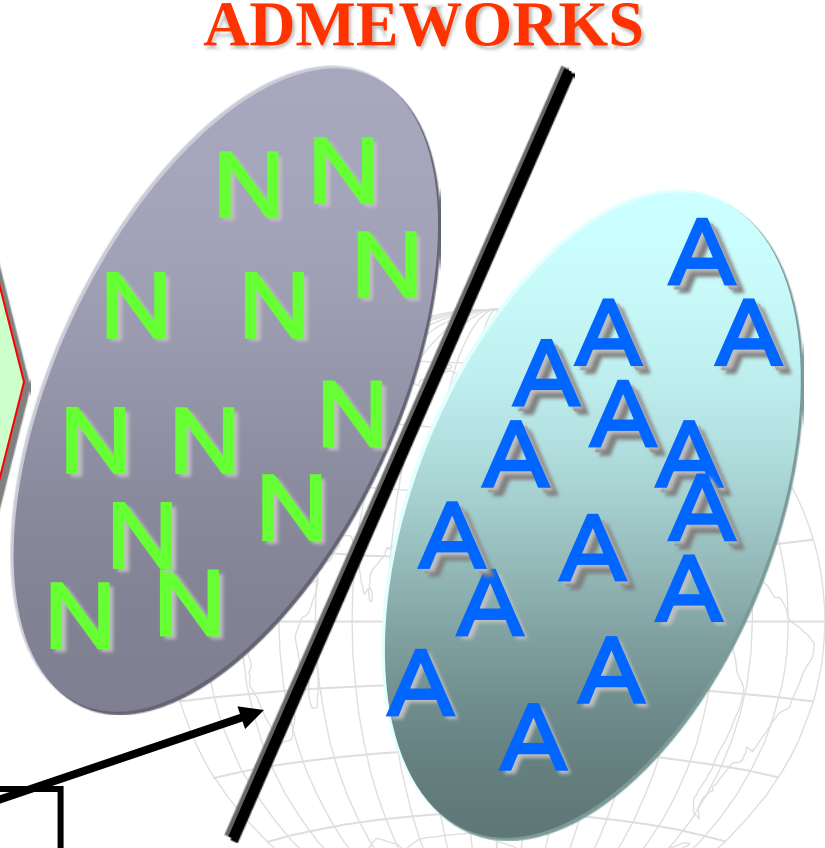
Simple classification and scientific classification

Pattern space impossible to be classified by linear discriminant



Pattern space classified by linear discriminant

ADMEWORKS



Feature selection

Neural network

Recursive partitioning

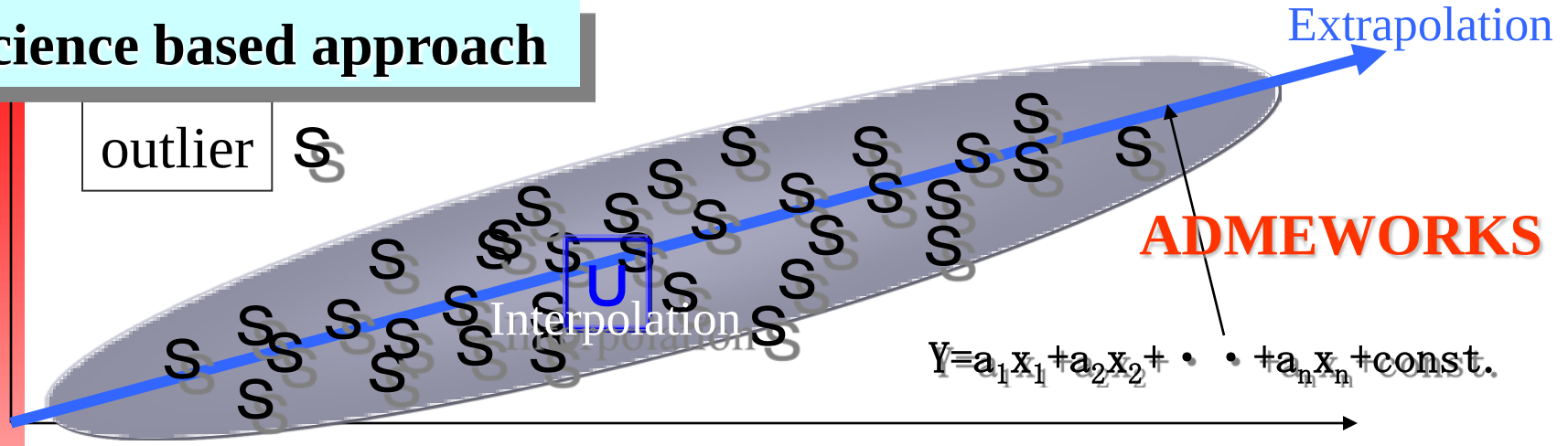
Linear discriminant

Classified by pattern space

Classified by scientific reasons

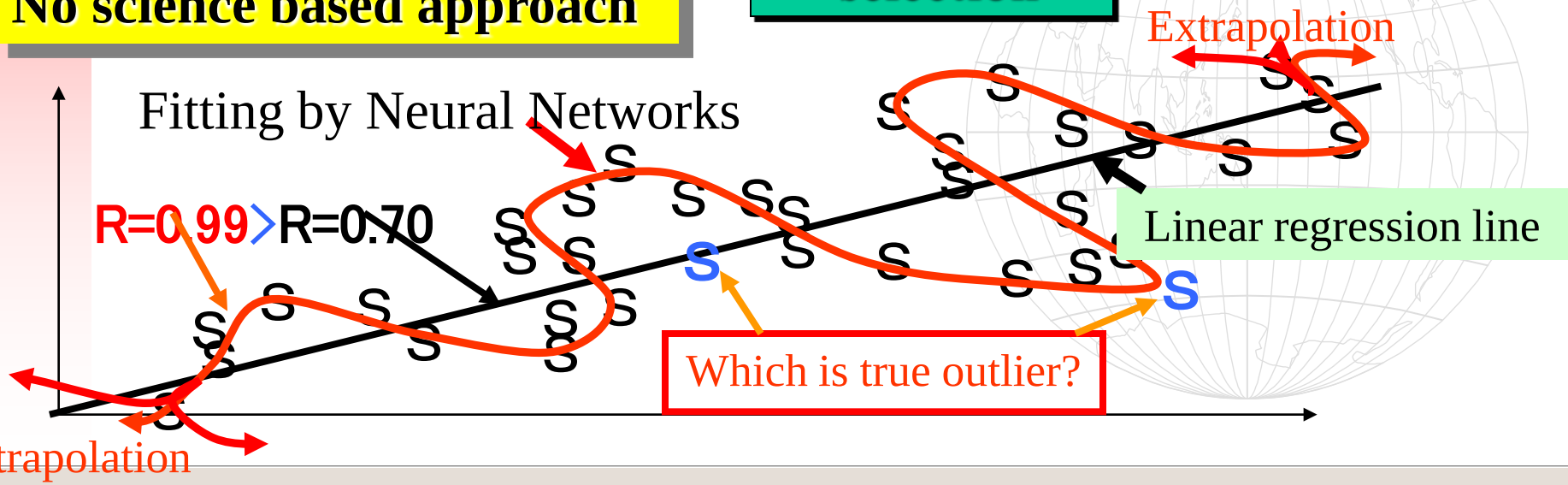
Simple fitting and scientific fitting

Science based approach



Feature selection

No science based approach



1 *"Integrated" concept*

2 *Application pattern of integrated concept*
"Integrated in silico screening"
"Integrated in silico drug design"

3 *Multivariate and pattern recognition*
pattern analysis and scientific analysis

4 *System overview*
ADMEWORKS:Prediction system
ModelBuilder:Chemical data analysis system

5 *Predictive models*

The system concepts and system requirements

(1) **Support various types of researchers & research fields**
Types of researchers : bench chemists, data analysts, informaticians
Research fields : drug exploration, drug development, drug metabolism, drug safety and drug informatics

(2) **Two dedicated systems**
Prediction system ; ADMEWORKS
Chemical data analysis system ; ModelBuilder

(3) **Two different types of predictive models**
Ready-to-use predictive models
Custom predictive models from proprietary data

(4) **Accessibility of systems**
Web client server system : access by anywhere & any time

(5) **Data analysis power**
Powerful data analysis engine :ADAPT (Developed by Professor P.C.Jurs)

(6) **Systems operate on personal computers**

In silico screening
In silico drug design

Chemical data analysis

ADMEWORKS

ModelBuilder

Custom-made models

a) GUI development
b) Interface w/ Model Builder
c) Batch processing
d) Runs on PC
e) Web client server

a) GUI improvement
b) Interface with ADMEWORKS
c) Runs on PC

ADAPT

(Automated Data Analysis and Pattern recognition Toolkit)

Data analysis engine

ADMEWORKS

Purpose :

In silico screening

Types of Models :

a) Ready-made predictive models

b) Custom-made models generated by ModelBuilder

Features :

High throughput parallel and virtual screening

ModelBuilder

Purpose :

a) Chemical data analysis

b) Generate predictive models for ADMEWORKS

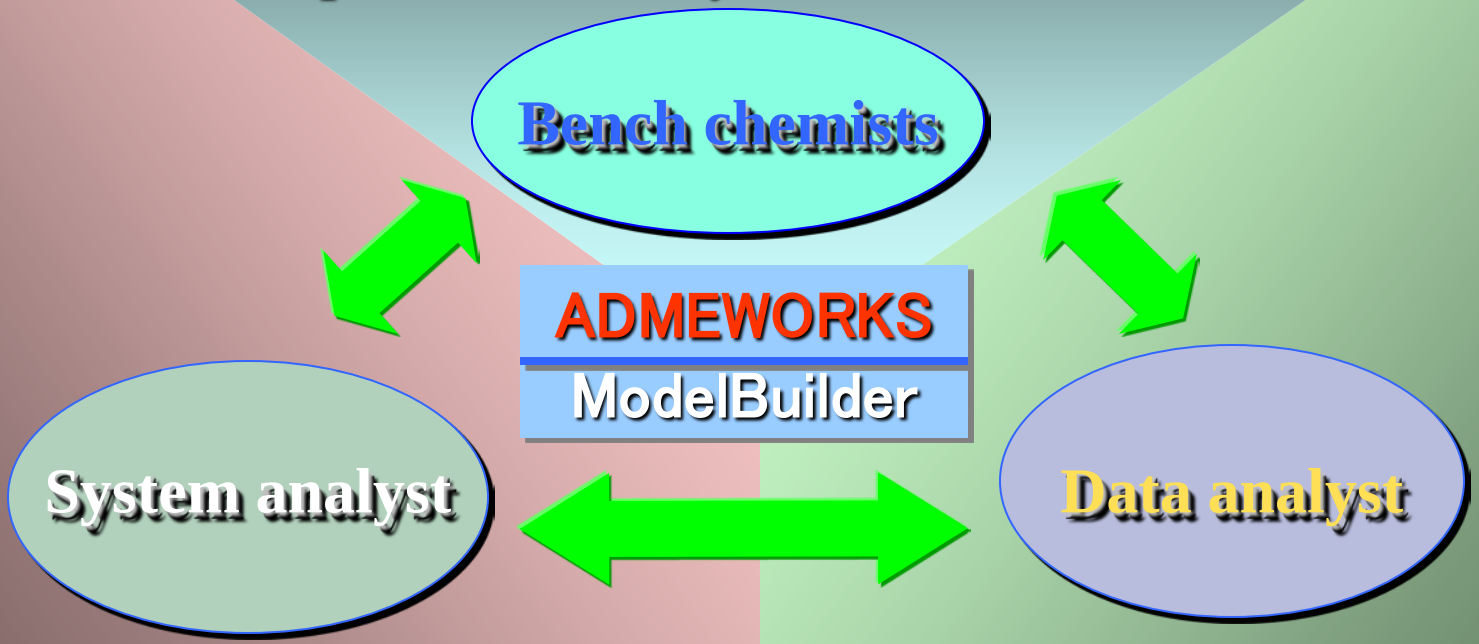
Features :

a) Build quantitative/qualitative predictive models

b) Structure-activity relationship studies, and drug design

What types of researchers will use system

1. Predict activity/ADME/toxicity/physicochemical property all in the same way using just one system
2. Make predictions anytime



1. Manage huge amounts of data
2. Achieve high-level security
3. Cut down on system maintenance

1. Experience world-class analytical tool (ADAPT)
2. Generate custom models using in-house data

1 *"Integrated" concept*

2 *Application pattern of integrated concept*
"Integrated in silico screening"
"Integrated in silico drug design"

3 *Multivariate and pattern recognition*
pattern analysis and scientific analysis

4 *System overview*
ADMEWORKS:Prediction system
ModelBuilder:Chemical data analysis system

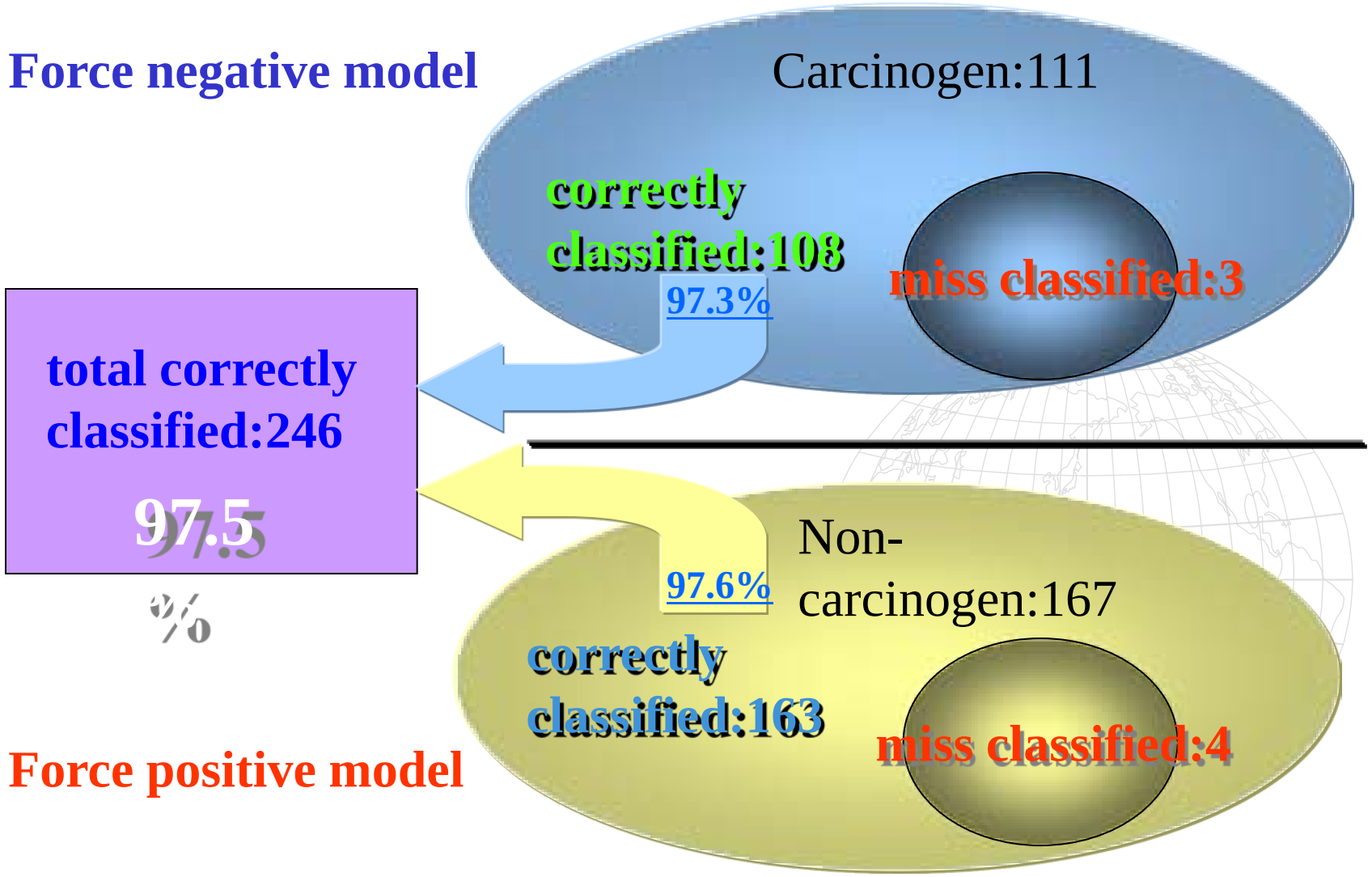
5 *Predictive models*

Model 1: False Negative Model

Sensitivity（発ガン性正答率）	97.3%	False Negative	2.7%
Specificity（非発ガン性正答率）	55.7%	False Positive	44.3%

Model 2 : False Positive Model

Sensitivity（発ガン性正答率）	31.5%	False Negative	68.5%
Specificity（非発ガン性正答率）	97.6%	False Positive	2.4%


Force negative model
Carcinogen:111
correctly classified:108
97.3%
miss classified:3
total correctly classified:246
97.5
%
97.6%
Non-carcinogen:167
correctly classified:163
miss classified:4
Force positive model

Ready-made predictive models available as of 2004.09

1. Toxicity related models

a) Carcinogenicity models (Male Rat data from NTP(1))

b) Ames test models (Collaborative research with NIHS(2))

2. ADME related models

P450 Inhibitor/Ligand predictive model (CYP3A4)

3. Physicochemical properties

a) Aqueous Solubility

b) LogP by MLOGP program

(1) National Toxicology Program (U.S.A.)
(2) National Institute of Health Science (Japan)

Ready-made models on schedule to be released next year

1. Toxicity related models

a) Ames test models: samples about 3000 compounds

(Collaborative research with NIIH(1))

b) Genotoxicity model (Collaborative research with NIHS(2))

c) Bio degradation and Bio accumulation

(Collaborative research with Fraunhofer(3))

2. ADME related models

a) Transporter prediction model (P-Glycoprotein):

samples about 200 / 1000 compounds

(Collaborative research with Professor Ishikawa at TIT(4))

b) Bio oral availability prediction model

(1) National Institute of Industrial Health (Japan) (2) National Institute of Health Science (Japan)

(3) Fraunhofer Institute (Germany) (4) Tokyo Institute of Technology (Japan)

Thank you very much for your attention.

INTEGRATED INSILICO SCREENING AND DRUG DESIGN SYSTEM

ACTIVITY, ADME, TOXICITY, PROPERTY ANALYSIS AND PREDICTION

Kohtaro Yuta[1], Jose Martin Ciloy [2], Masato Kitajima[2], Wojtek Plonka[3] and Munetaka Sawada[1]

1.Fujitsu Ltd., 2.Fujitsu Kyushu System Engineering Ltd., 3. FQS Poland Sp. z o.o.

FUJITSU

THE POSSIBILITIES ARE INFINITE