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*IUPAC CHEMRAWN XVI at 2003*

# ***Innovation in the Japanese Chemical Industry***

*August 9-12, 2003*

**Makoto Imanari**
*Chief Technology Officer*
*Mitsubishi Chemical Corporation*

# Outline of Presentation

- Session-1: The Japanese Government's Plans
- Session-2: The Reformation, Renovation and Topics in Mitsubishi Chemical Corporation
- Session-3: Examples of computer simulation for R&D speed up in MCC

# *Session-1*

## *The Japanese Government's Plans*

# *Science and Technology Policy*

| [ Main Issues] | [ Countermeasures ] |
| --- | --- |
| A. R&D doesn't lead directly to strengthening of competitiveness | Economy Activation Project |
| B. Lack of human resources (managers) with MOT sense and skills | Nurturing of human resources (managers) with MOT sense and skills |
| C. Hoarding of "R&D fruits" | Promotion of spin-off venture businesses |
| D. Indispensability of activation of fundamental R&D institutes such as universities | Reformation of competitive fund system and academia |
| E. Necessity of government budget execution in accordance with R&D characteristics | Through performance-related evaluation agile and flexible budget execution |
| F. Lack of industry's MOT innovation model responding to a new age | Presentation of MOT innovation model |

Ref: Report of Hiramura Minister in April 4, 2003

# Nurturing of human resources with MOT sense and skills

[ Main Issues]

* Lack of technology management systems in industries

  * Necessity of good technology judge and industrialization strategy

    * Over 200 MOT courses and about 10 thousand graduates of MOT per year in US

    * MOT Programs started by some institutes in Japan

[ Action Plans ]

* Nurturing of about 10 thousand managers with MOT sense and skills

In METI

Support of 39 institutes such as universities being intended to establish MOT courses from FY 2002 supplementary budget

Ref: Report of Hiramura Minister in April 4, 2003

# *Reform of Competitive Fund System and Academia*

[ Main Issues ]

Penetration of competition principle and activation of creative power

[ Action Plans ]

* Reformation of competitive fund system which maximize researchers' creativity

* Academia reformation

  * Complete liberalization of establishment of universities, departments and student capacity

  * Consolidation of outside evaluation organization

In METI

Introduction of Program directors in competitive fund execution etc.

Ref: Report of Hiramura Minister in April 4, 2003

# Prioritization of Science and Technology

Establishment of economy activation project directly linked with commercialization (Focus 21) Total 36.7 billion \ in FY 2003 budget

**Life science:** 8.8 billion \

* Sugar chain engineering PJ
* Bio-IT fused instrument development PJ etc.

**Environment :** 4.4 billion \

* Next generation energy saving PDP PJ
* High functional materials applied to houses utilizing photo-catalysis PJ etc.

**Information and telecommunication :** 17.3 billion \

* IT based advanced software development PJ
* Chips for semiconductor application PJ etc.

**Nanotechnology and materials :** 6.1 billion \

* Carbon nanotube FED PJ
* Ultimate function of Diamond PJ etc.

Ref: METI Report of Focus 21

# *Session-2*

## *The Reformation, Renovation and Topics in Mitsubishi Chemical Corporation (MCC)*

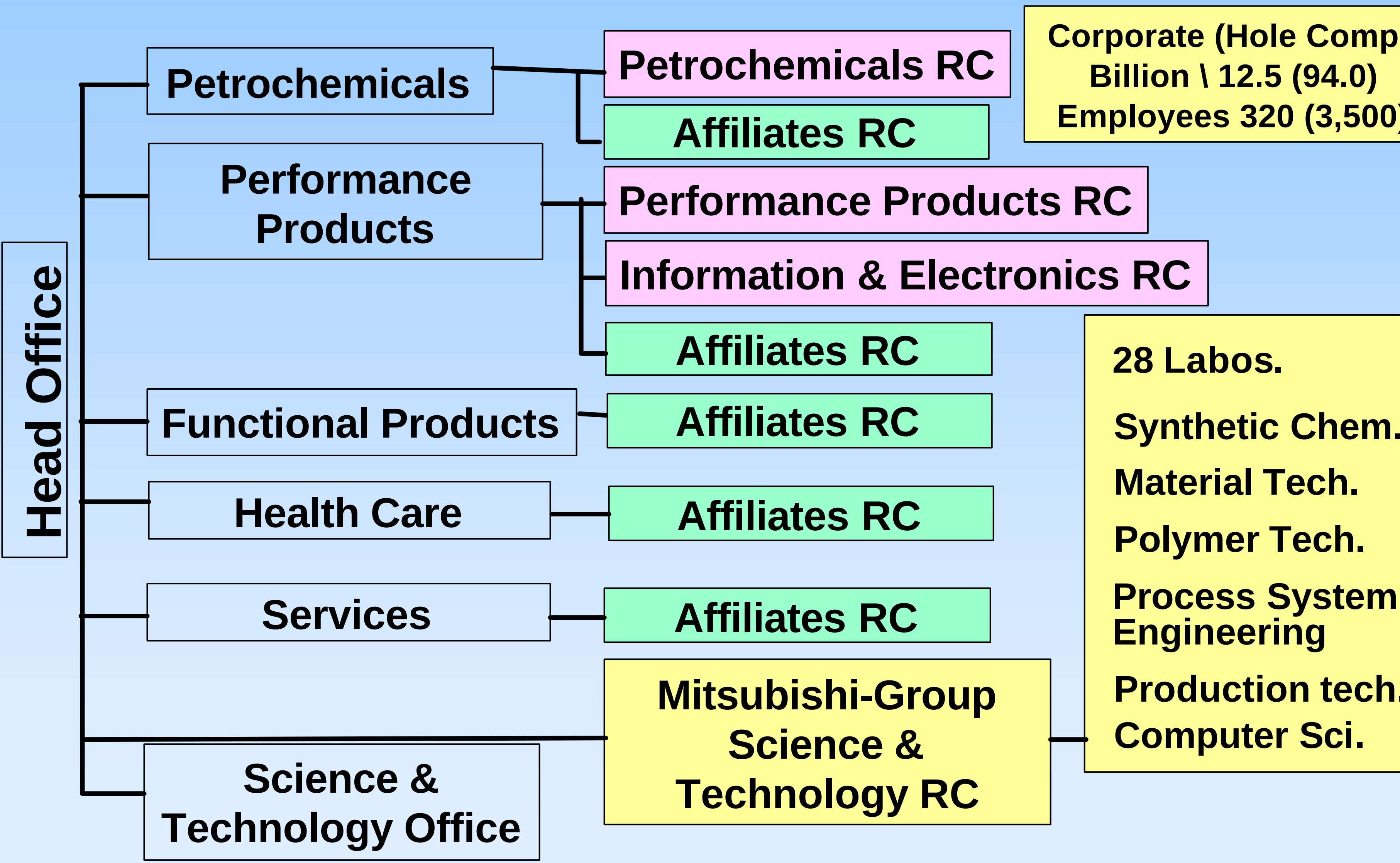
# Corporate Profile of MCC



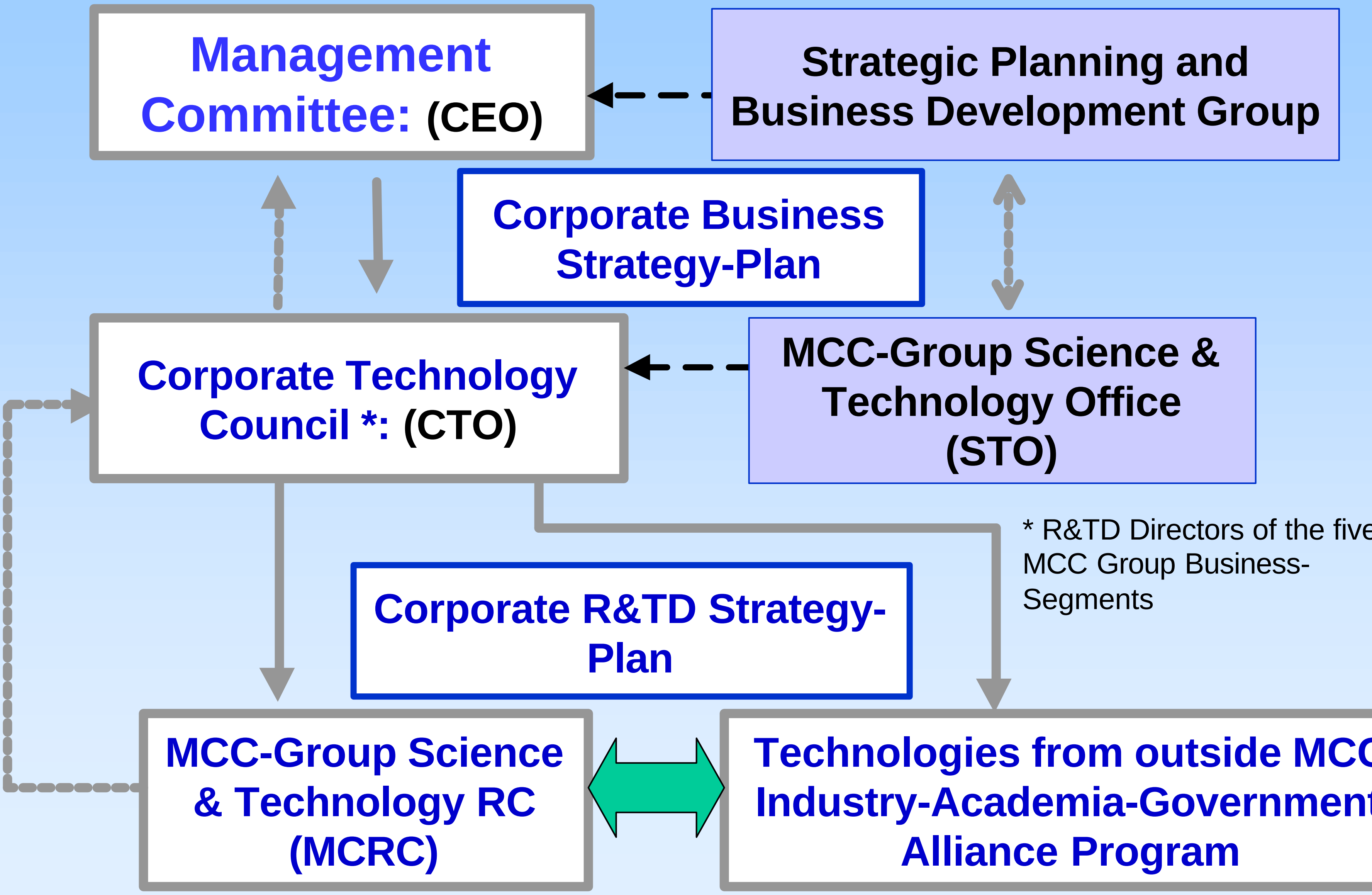
| | |
|---|---|
| **Company Name** | Mitsubishi Chemical Corporation |
| **Head Office** | 5-2, Marunouchi 2-chome, Chiyoda-ku, Tokyo 100-0005 |
| **Capital** | 145.1 Billions of yen on March 31, 2003 |
| **Representatives** | Chairman of the Board: Kanji Shono<br>President & CEO: Ryuichi Tomizawa |
| **Number of Employees** | 7,853 members on March 31, 2002 |
| **Net sales**<br>**Consolidated**<br>**Non-consolidated** | <br>1,887.5 Billions of yen<br>674.6 Billions of yen<br>For the Year Ended March 31, 2003 |

**Head Office**
(Mitsubishi Building)

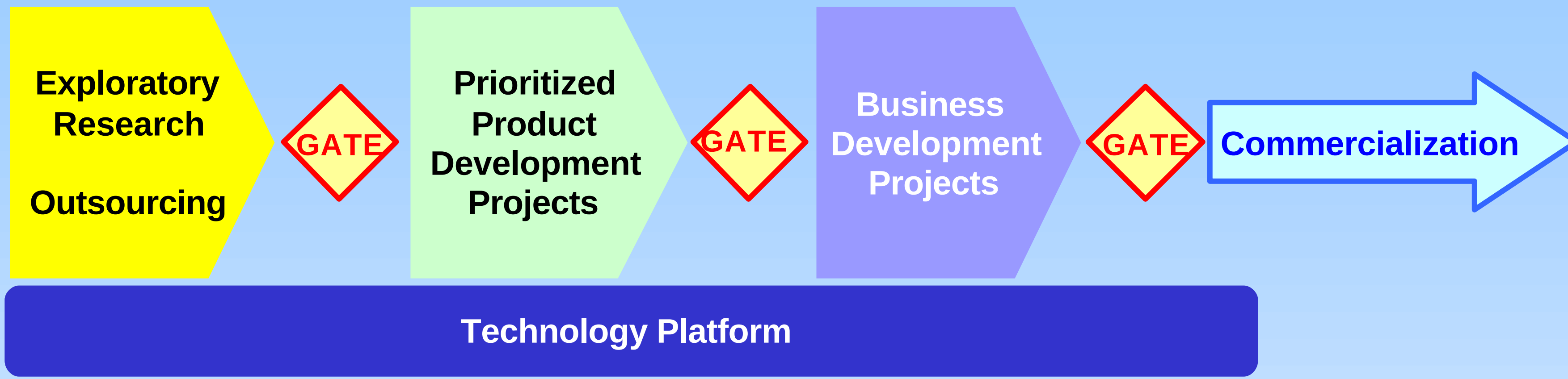
# R&TD Organization of MCC Group



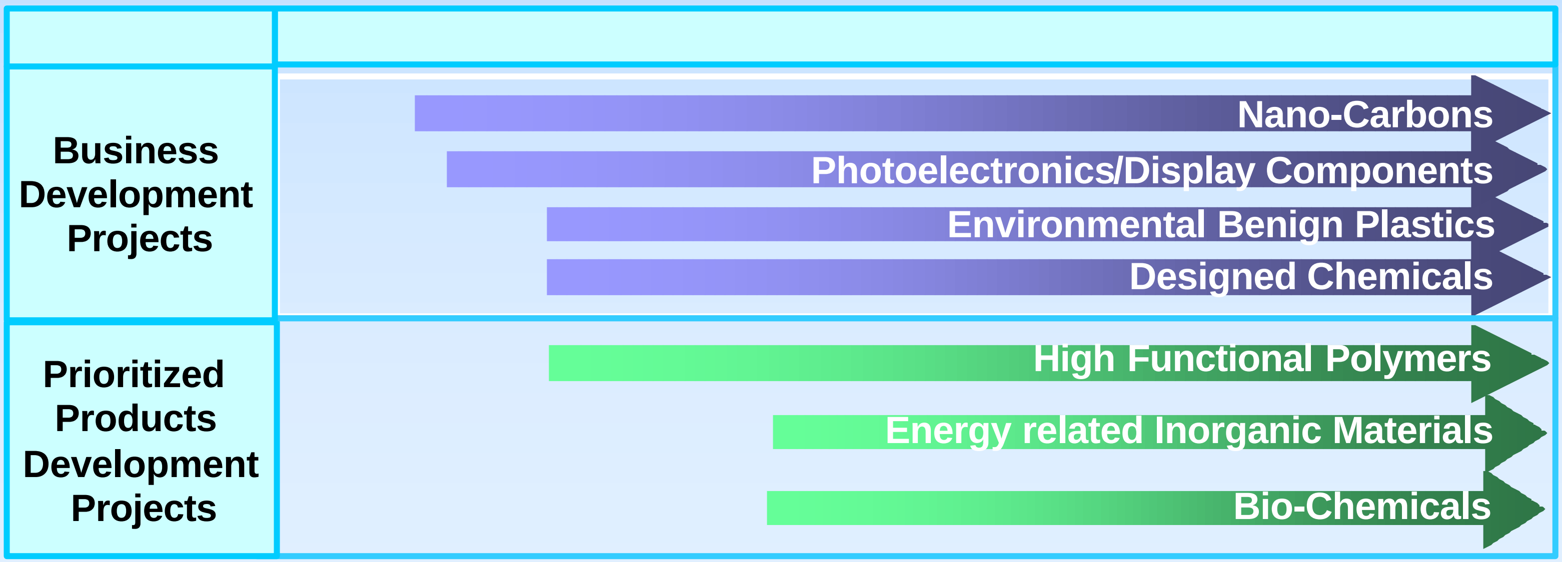
# Aligning R&TD with Business Strategy



# Stage Gate System and Corporate R&TD Pipeline



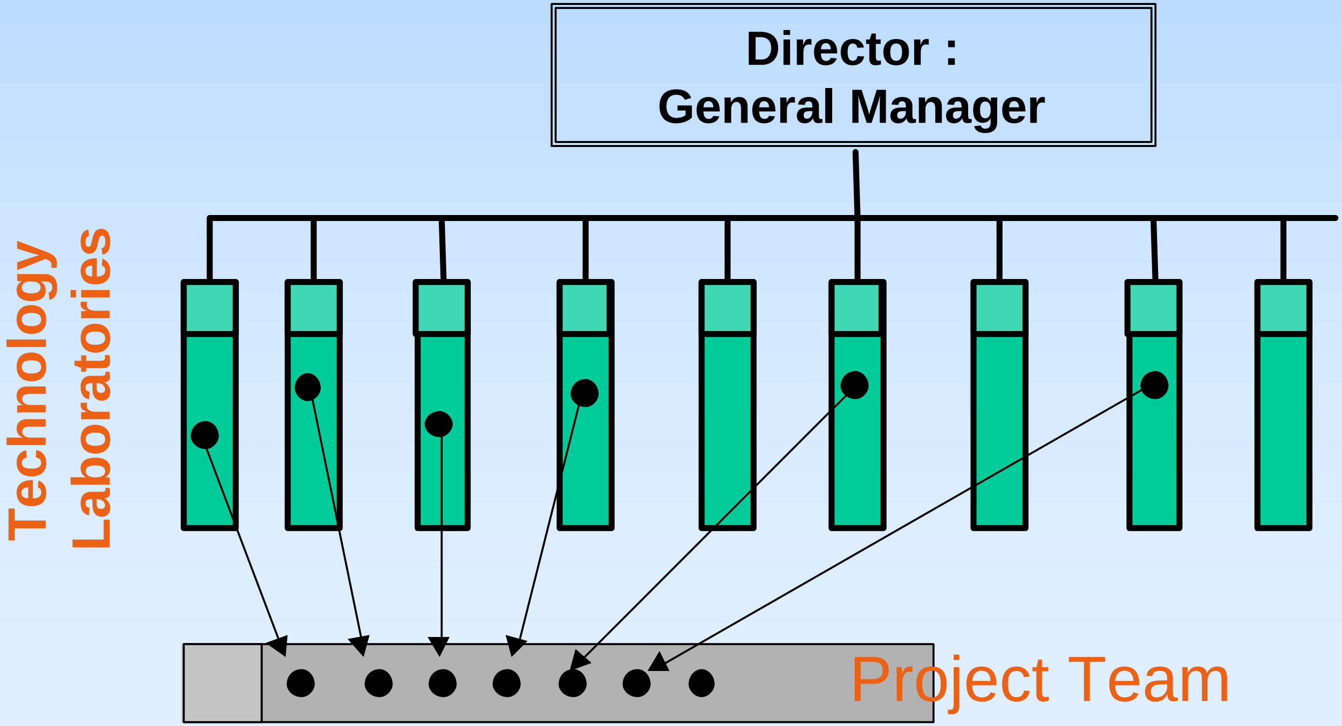

## Pipeline Examples



# R&TD Acceleration by Project Team

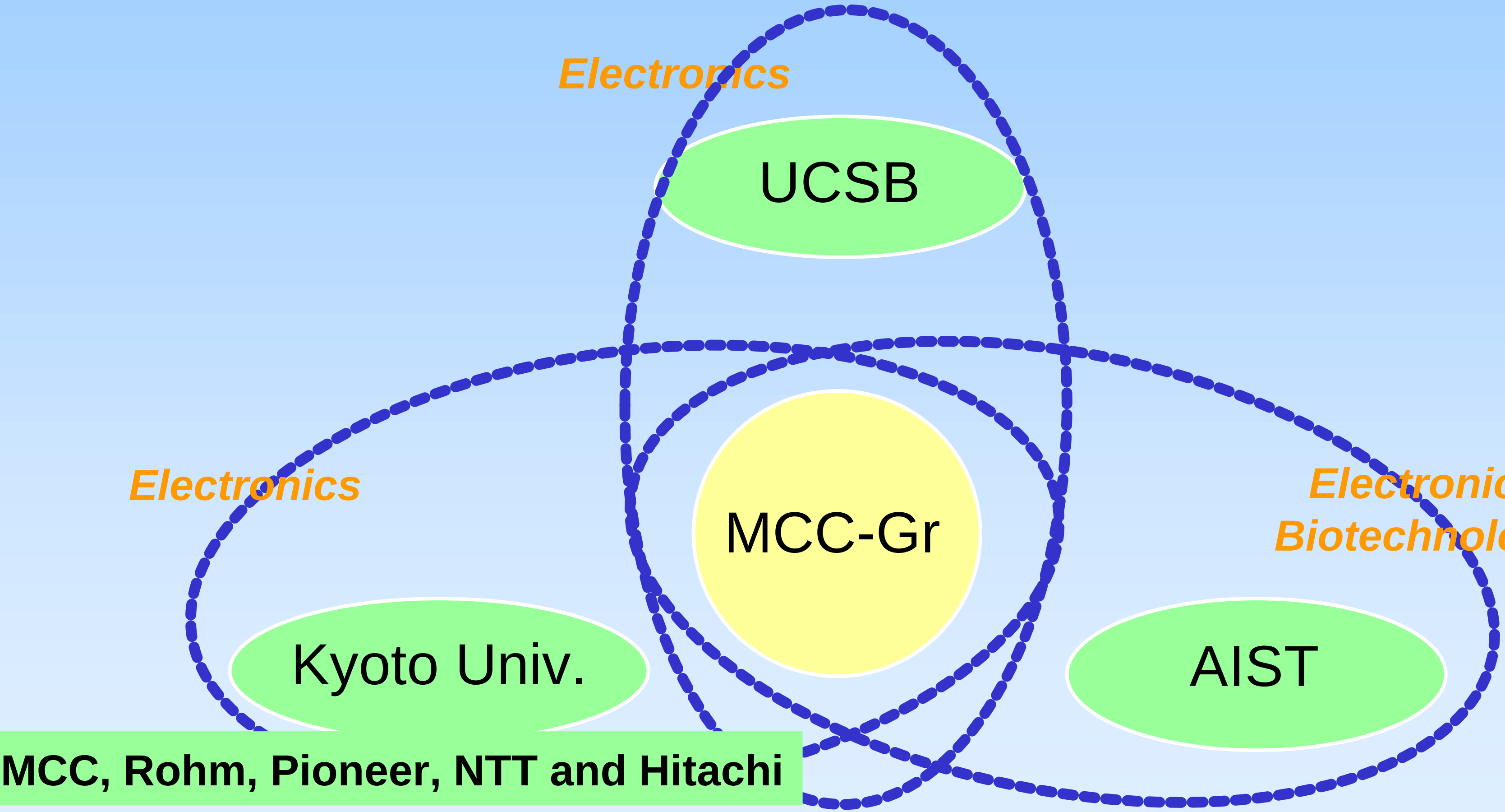
**The project team is composed of several researchers who belong to technology laboratories and have necessary technologies.**

The mission of Project teams is to create new products and processes and improve existing products, processes and technology platforms etc.



# *Academia and Outer Institute Alliances in Information-electronics and Biotechnology*

Development of new materials and devices




*Cross organizational "Virtual" research institutes*

# *Session-3:*

## *Examples of computer simulation for R&D speed up in MCC*

# Model-Based Solvent Selection and Protein Crystalliz

J.-W. Shen, S. Nakamura, H. Asatani, P. Kolar, H. Nakata, A. Tsubo

*MCC-Group Science & Technology Research Center*

**S. Sugio**

*ZOEGENE Corporation*

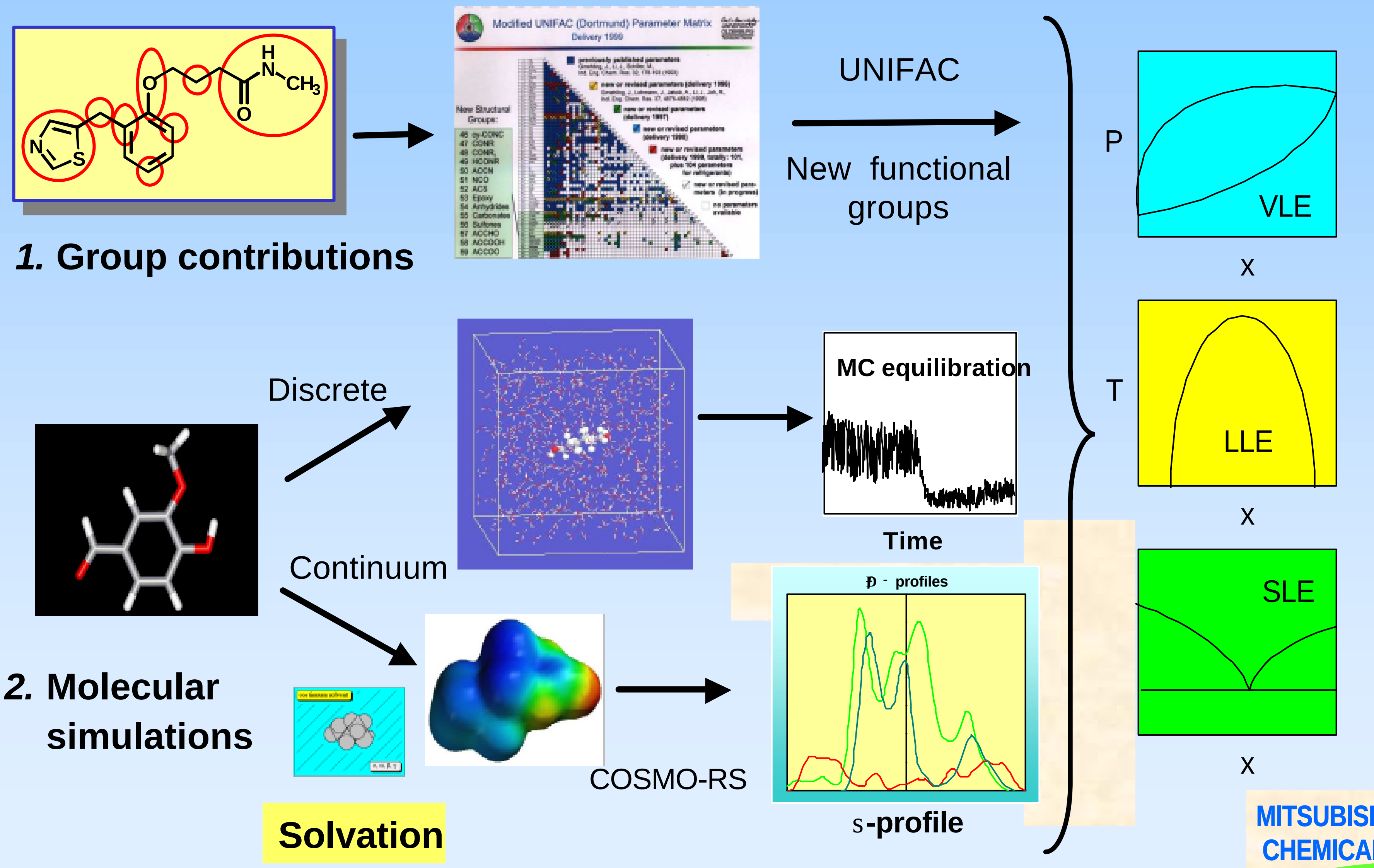
**Objective:**

**Minimization of HT screening experiments using modeling techniq**

**Examples:**

1. **Solvent selection - Resolution of diastereomers**
2. **Model-based protein crystallization**

# Solubility Prediction Methods

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# *Example* - Resolution of Diastereomer Salts

- **Reactive crystallization:**

**A + B**

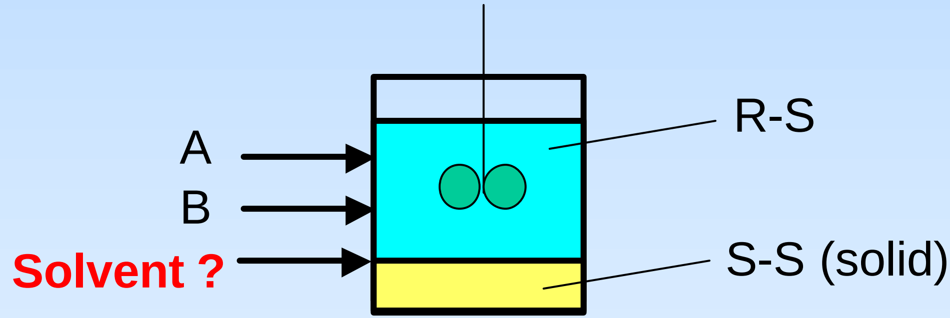
**R(-)** **S(+)** **S(+)**

**Similar solubilities**

**R(-).B** (R-S) **High solubility**

**S(+).B** (S-S) **Low solubility**

(Desired product)




**Task: Find a solvent which maximizes R-S / S-S solubility difference**

**COSMO-RS prediction method**

# COSMO-RS Prediction of Selectivity

| Solvent | S-S | R-S | $S_{ij}$ (S/R) |
|---|---|---|---|
| | $\gamma$ .... | $\gamma$ .... | |
| Paraffines | 690.4 | 33.7 | 20.48 |
| | 618.5 | 30.3 | 20.42 |
| | 590.9 | 29.1 | 20.32 |
| | 615.9 | 30.4 | 20.24 |
| | 937.2 | 46.4 | 20.20 |
| | 471.1 | 23.3 | 20.18 |
| | 869.2 | 43.1 | 20.17 |
| | 424.3 | 21.1 | 20.12 |
| | 774.4 | 38.5 | 20.12 |
| | 711.5 | 35.4 | 20.08 |
| | 563.1 | 28.2 | 19.99 |
| | 637.6 | 31.9 | 19.96 |
| Aromatics | 20.6 | 2.2 | 9.48 |
| | 20.1 | 2.1 | 9.39 |
| | 17.9 | 2.0 | 9.10 |
| | 15.2 | 1.7 | 9.06 |
| Alcohols | 0.3 | 0.2 | 1.51 |
| | 0.8 | 0.7 | 1.22 |
| | 1.4 | 2.0 | 0.71 |

$S_{ij}$

**Separation selectivity:**

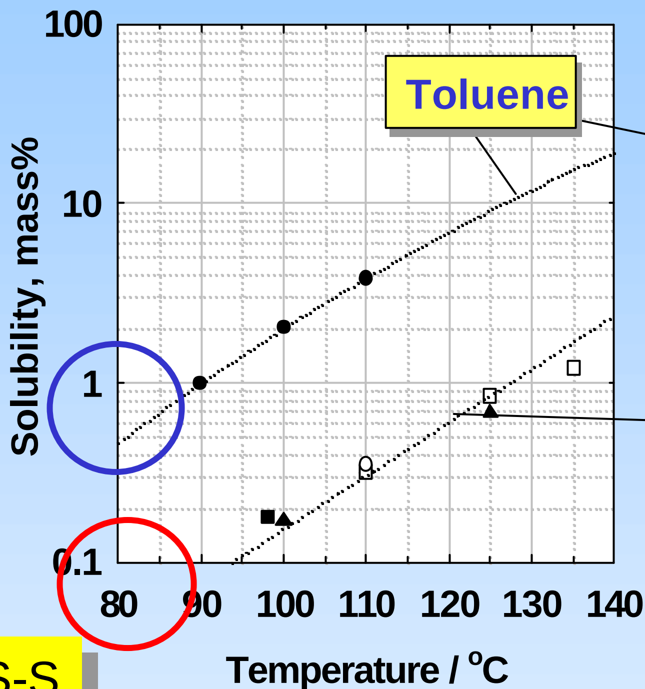
$$S_{ij}\,(S/R) = \gamma_{S\text{-}S} \,/\, \gamma_{R\text{-}S}$$

$\gamma_i$ - Activity coefficient (COSM

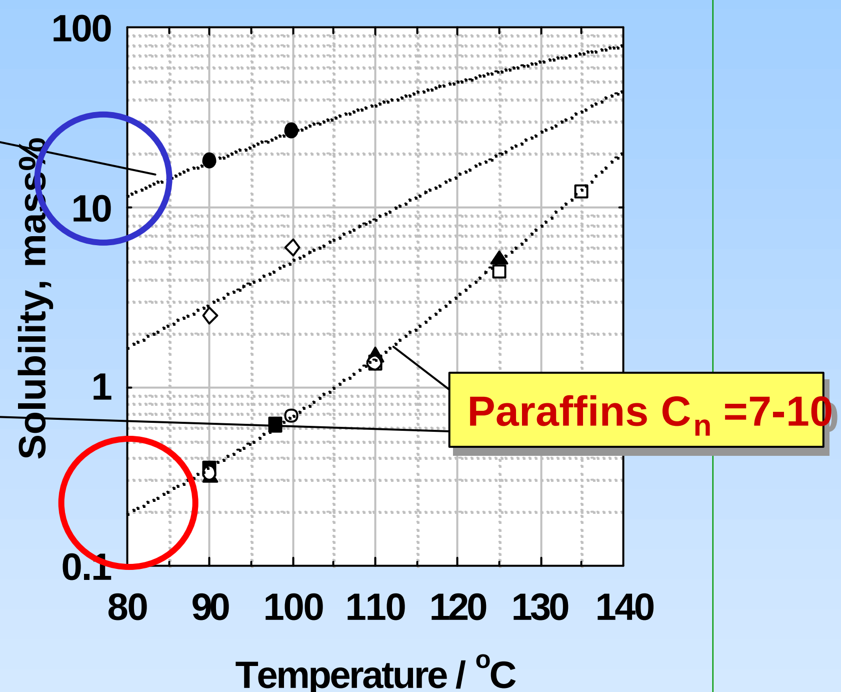
Paraffins vs. Aromatics

- Higher S/R differenc
- Lower S-S solubility

# Experimental Validation




*a)* **Solubility of S-S**



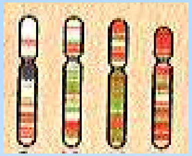

*b)* **Solubility of R-S**

Lower S-S solubility

# From Biology to Chemical Engineering

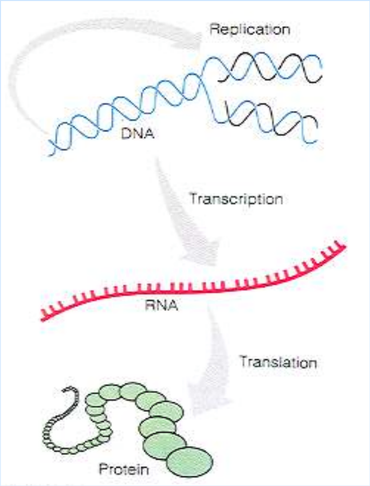
**Biology** → **Chemistry** → **Chemical Engineering**

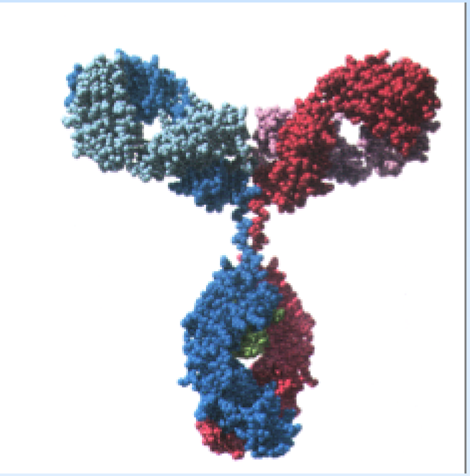
- Central Dogma
  (DNA --> Proteins)
- Protein functions



- Genome Science
  (Sequencing)
- Product design

- Process development
- Modeling and simulation

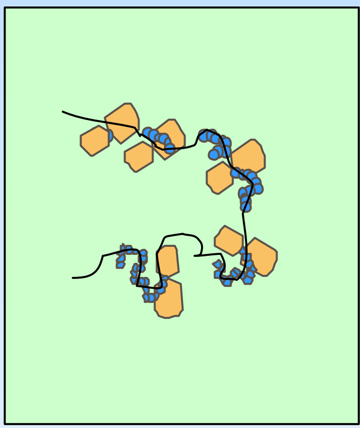


# Example: Protein Crystallization

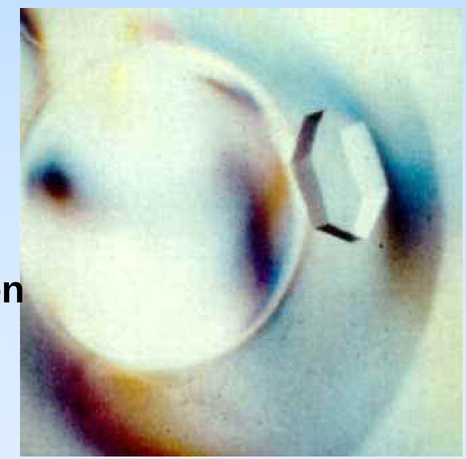
mRNA → **Protein Synthesis** → Purification → **Protein Crystallization** → Crystal → **Protein 3D structure determination**

( Bottleneck in proteomic pipeline)



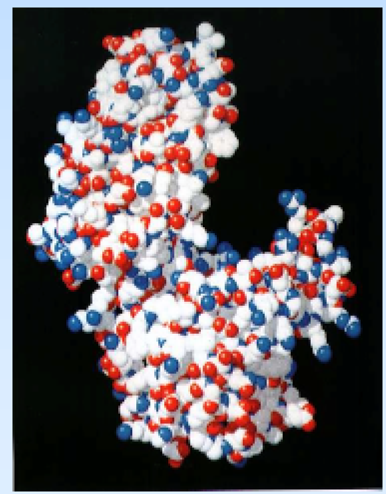
(Cell-free) protein expression

Purification → Crystallization



Protein single crystal (> 0.1 - 0.3 mm)

X-ray diffraction → Synchrotron



Protein structure

# Model-Based Protein Crystallization

**Synthesized protein**

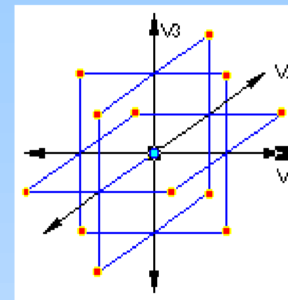
**IN**

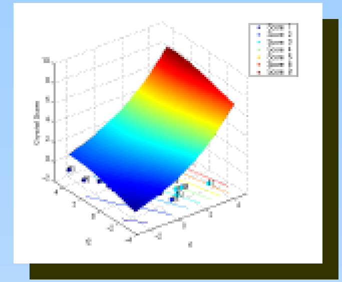
**Theory / Know-how**

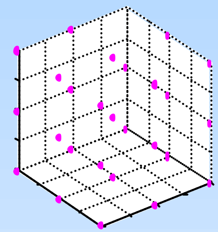
**Crystallization Modeling**

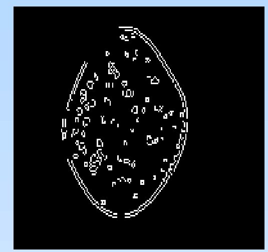
**Experiment** (HTS)

**Design of experiments** (DOE)







**Protein crystals**

**OUT**

**Protein 3D structure determination**

**Model-Based Protein Crystallization**

# Reaction Analysis Example of Pharmaceutical Intermediate


Substrate Product Byproduct

? Background ?

? Low yield
? Unknown byproduct
? Low conversion

? Objective ?

**To increase product yield**

? Work Flow ?

1) Reaction Experiments → **Micro Flow Reactor**

Reaction analysis tool for rapid reaction(1sec~ )

2) Determination of Reaction Mechanism → **In-situ IR&Chemometrics**

Combination of chemistry and mathematics

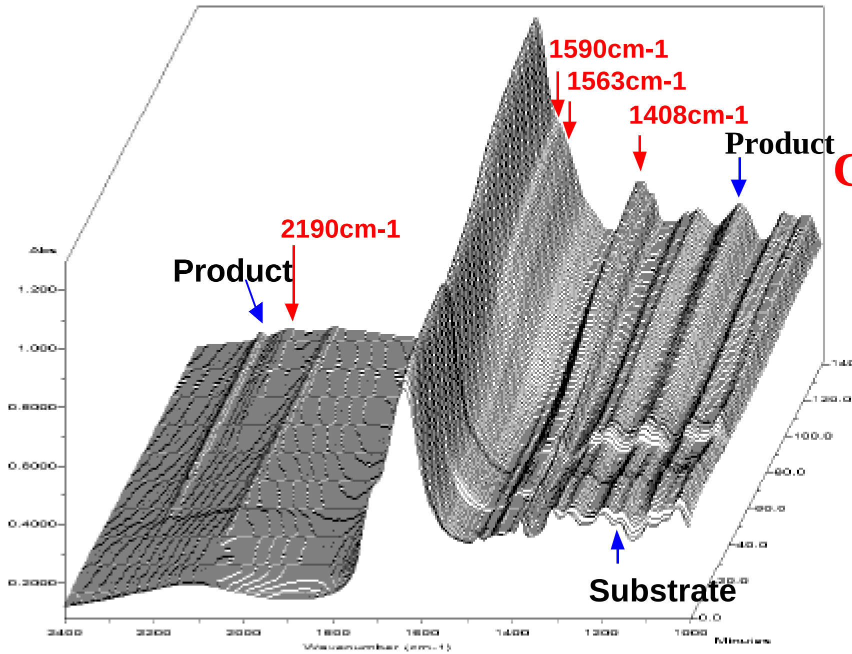
3) Kinetic Estimation → **Reaction Analysis Studio (RAS)**

4) Reactor Optimization → **Reaction Analysis Studio (RAS)**

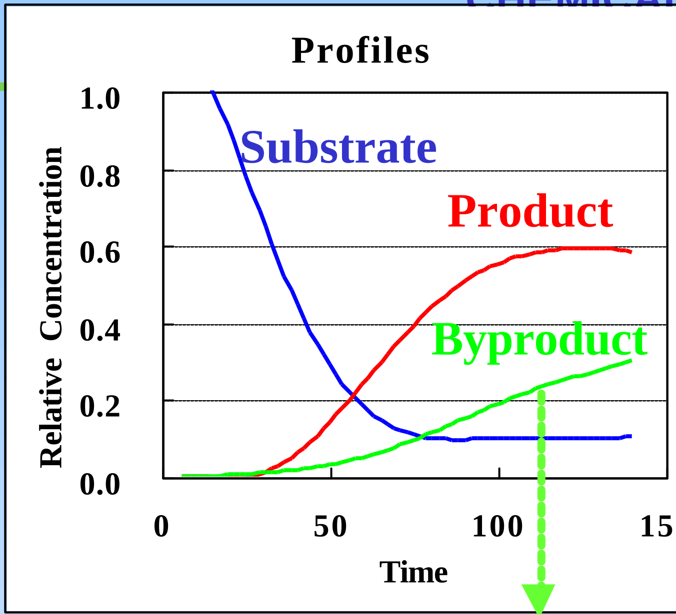
Software tool developed by MCC Optimization group in collaboration with CAPEC group in Denmark Technical University.

# Determination of Reaction Mechanism

## Reaction data ( by In-situ IR )

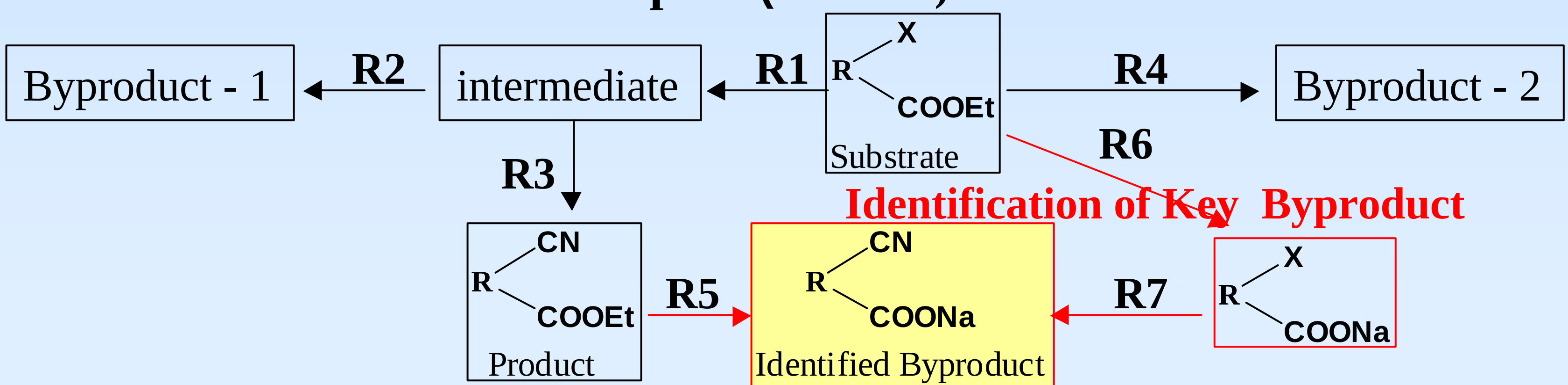



Chemometrics




**With extracted pure component spectrum, unknown byproduct is identified to Sodium Calboxylate**

## ? Determination of Reaction path ( R1~R7) ?



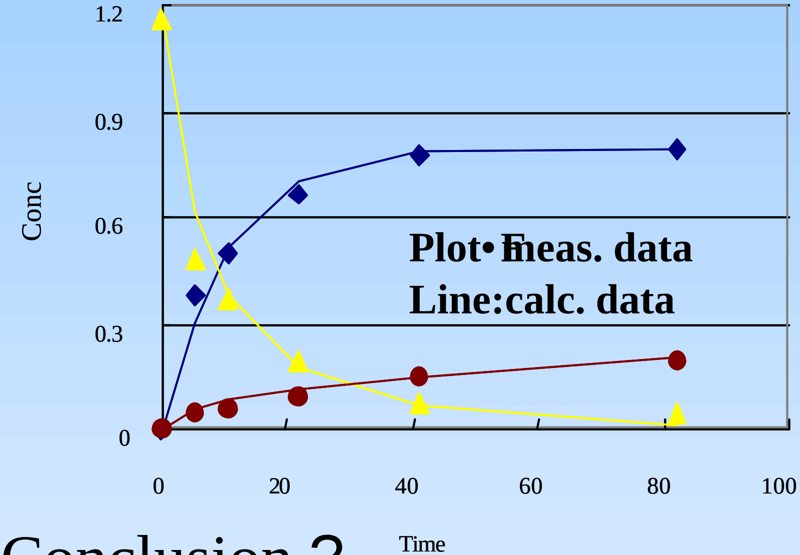
# Kinetic Estimation and Reactor Optimization( by RAS)

**Kinetic Estimation** → **Reactor Optimization**

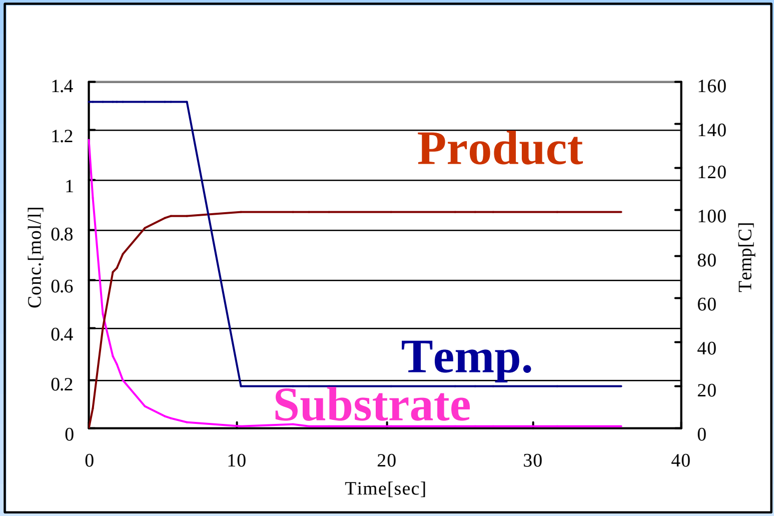
$$R1 = -k1 \cdot f([Sub], [NaCN], [Cat])$$

$$k1 = A \cdot \exp(-Ea / RT)$$

Parameter estimation




Dynamic optimization of control variables (temp, conc, etc.)




Increase of yield is achieved

## Conclusion ?

| | |
|---|---|
| Micro flow reactor | Accurate experiment for rapid reaction |
| In-situ measurement & Chemometrics | Determination of complicated reaction mechanism |
| Reaction analysis tool (RAS) | High performance kinetic estimation &optimization |

Developed an Effective Approach for R&TD Speed Up

# Summary

1. Japanese Government is now going to improve the science and technology policy.
2. Mitsubishi Chemical Corporation is now going to improve R&D policy
3. Mitsubishi Chemical Corporation has been succesfully utilizing many kinds of computer simulation technology for promoting R&D speed up

# Appendix

# *Target Image of Future Society and New Bioindustry*

-- Improvement of “Living”, “Eating”,”Inhabiting” --

imitations of 20th
entury technologies

ransformation of

. Health &
Longevity

. Food Supply

. Environment
& Energy

Breakthrough by new
Biotechnology

**Future Society**

**Living:Health & Longevity**

* BT diagnostics, medical care promotion
* Realization of both longevity & medical cost prevention

**Eating:Safety & Functionality**

* BT food industry promotion
* Simultaneous achievement of safety, high functionality & supply

**Inhabiting:Sustainable safe and secure society**

* Overcome environment & energy limitations
* Realization of profitable environmental industry

New Bioindustry (2010)
Over 1 million employees

**Medical Care 8,400 billion **

**Food 6,300 billion **

**Environ ment & Process 4,200 billion **

**Biological Tool & Information**

**Fusion of BT, IT, NT**

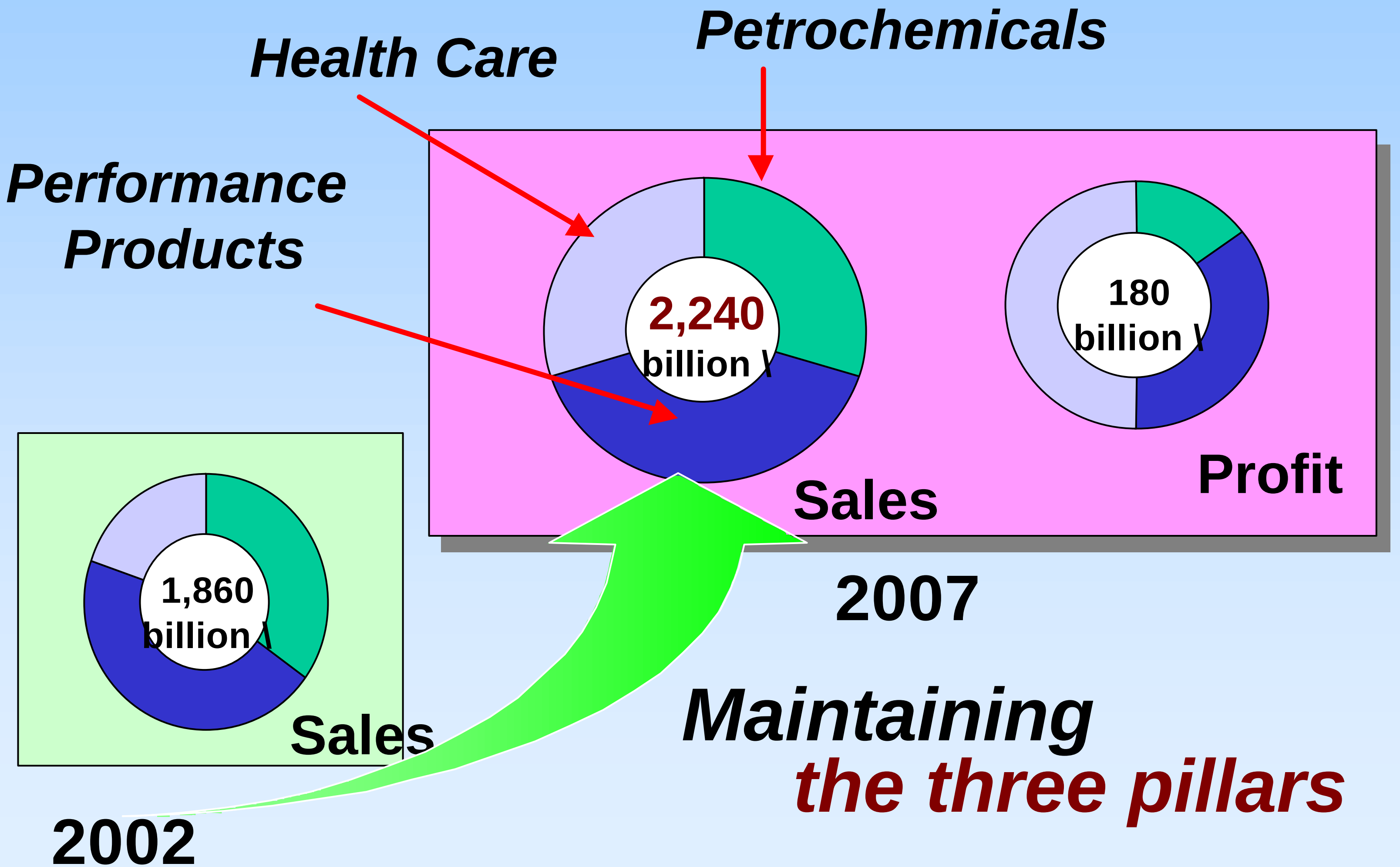
**5,300 billion**

**Strategy 1**
**Enhancement of R&D**

**Strategy 2**
**Fundamental strengthening of industrialization process**

**Strategy 3**
**Intensive understanding b**
**citizen**

# *Middle term Strategy of Mitsubishi Chemical Group*




***Maintaining the three pillars***

# *Strategic Alliance with Outer Institutes*

**Interdisciplinary collaboration**

**Exploratory research: Comprehensive alliances with leading universities and outer institutes such as UCSB, Kyoto Univ., AIST and Imperial College etc.**

**Promoted Alliance Strategy**

*** Promote comprehensive alliances in specific fields**

*** Establish alliance department in research institute and send responsible officials from MCC**

*** Accept individual themes under comprehensive theme (from the public)**

*** Bring research collaborators from MCC**

**Collaboration in strong and specific fields from early stage**

**Business development research: Alliance with business partners**

**Realization in integrated alliance with Kyoto Univ. and 5 companies**

# *Technology Programs and Pipeline of Future Products*

- **Areas of Focus**
  – Chemicals and Materials: "*Product-Innovation*"
    - Specialty Chemicals, Materials, and Components for the Information and Electronics Industry
    - Biochemicals and Biomaterials
    - "Specialty" Commodities: Organic and Inorganic
  – Services: "*Solution-Partnerships*"
    - Genomic Drug Discovery
    - "Designed" Chemicals
    - "Designed" Materials
- **The Pipeline of Future Products and their Economic Impact**

# Technology Programs



## "Green" Sustainable Plastics

Become the world-leader in a variety of elastomeric (soft) biodegradable polymers, produced from renewable resources

- **Technology Platforms**
  - **Metabolic Engineering for the low-cost production of monomers from renewable resources**
  - **Polymer design with desired properties**
  - **Unique**
- **Products**
  - **A broad variety for different applications**

# Bio-production of ‘GS Pla’ monomers

***Fossil resources***

n -Butane (Maleic anhydride) → ***Succinic acid***

1,3-Butadiene → ***1,4-Butanediol***

Post fossil resources

***Plant resources***
***ex. Corn, potatoes, etc.***

→ Glucose

Fermentation → *Lactic acid*
*established*

Fermentation → ***Succinic acid***

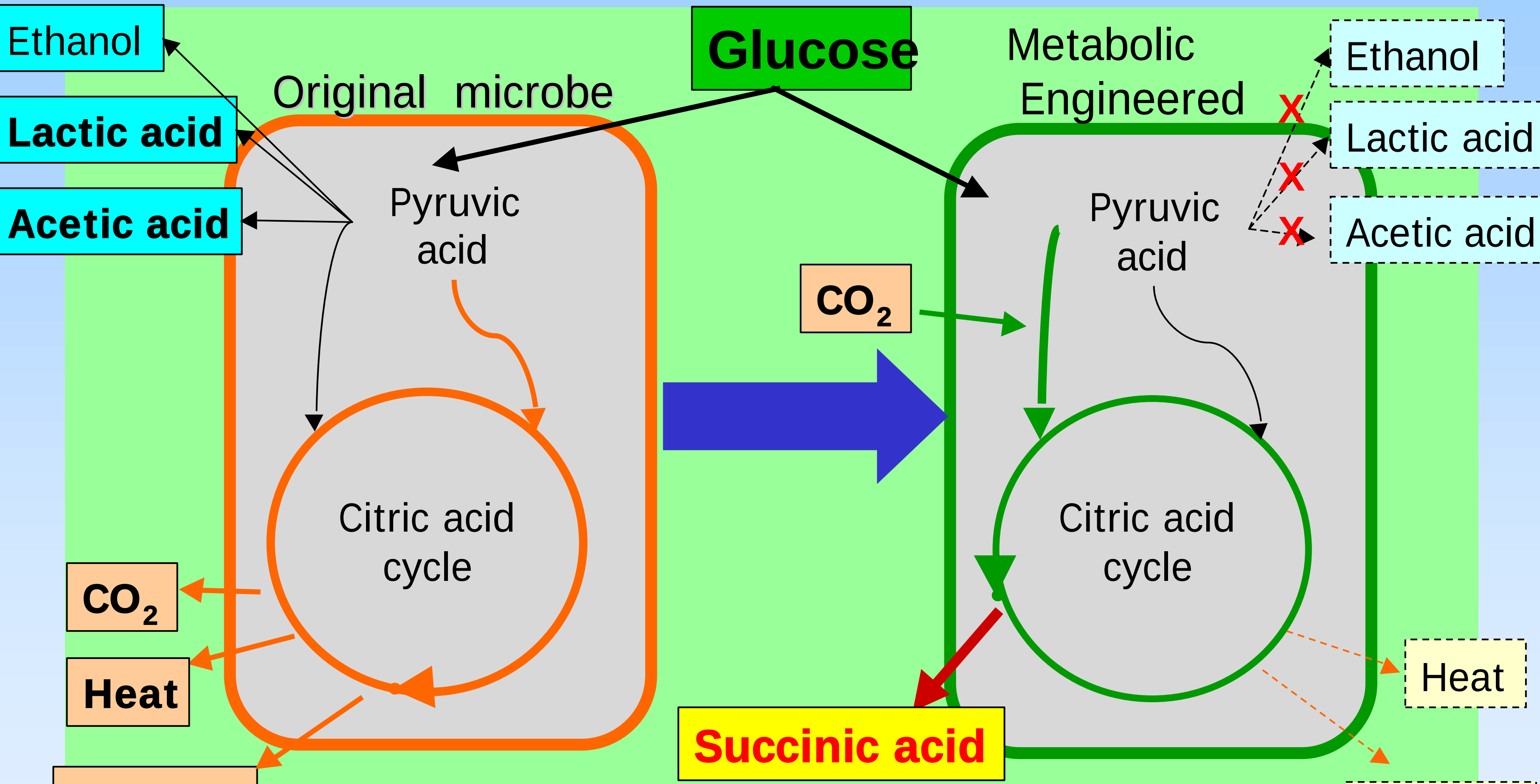
**CO2**

Hydrogenation

***1,4 -Butanediol***

*Appl Microbiol Biotechnol 1999*

# Succinic acid production
# - Metabolic Engineering-




**Enhance product formation and cut by-product with molecular breeding etc.**