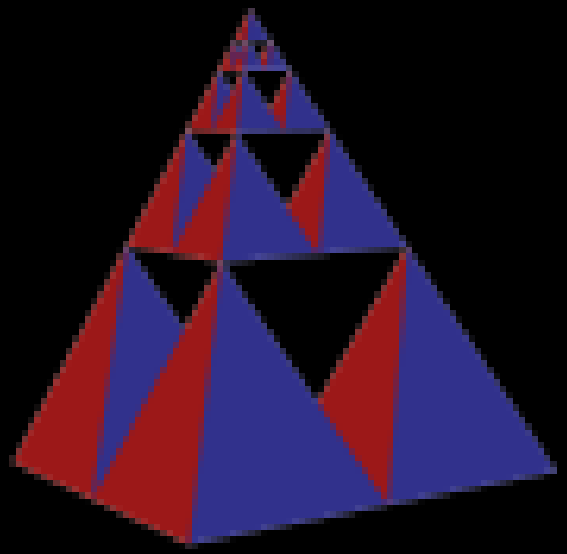
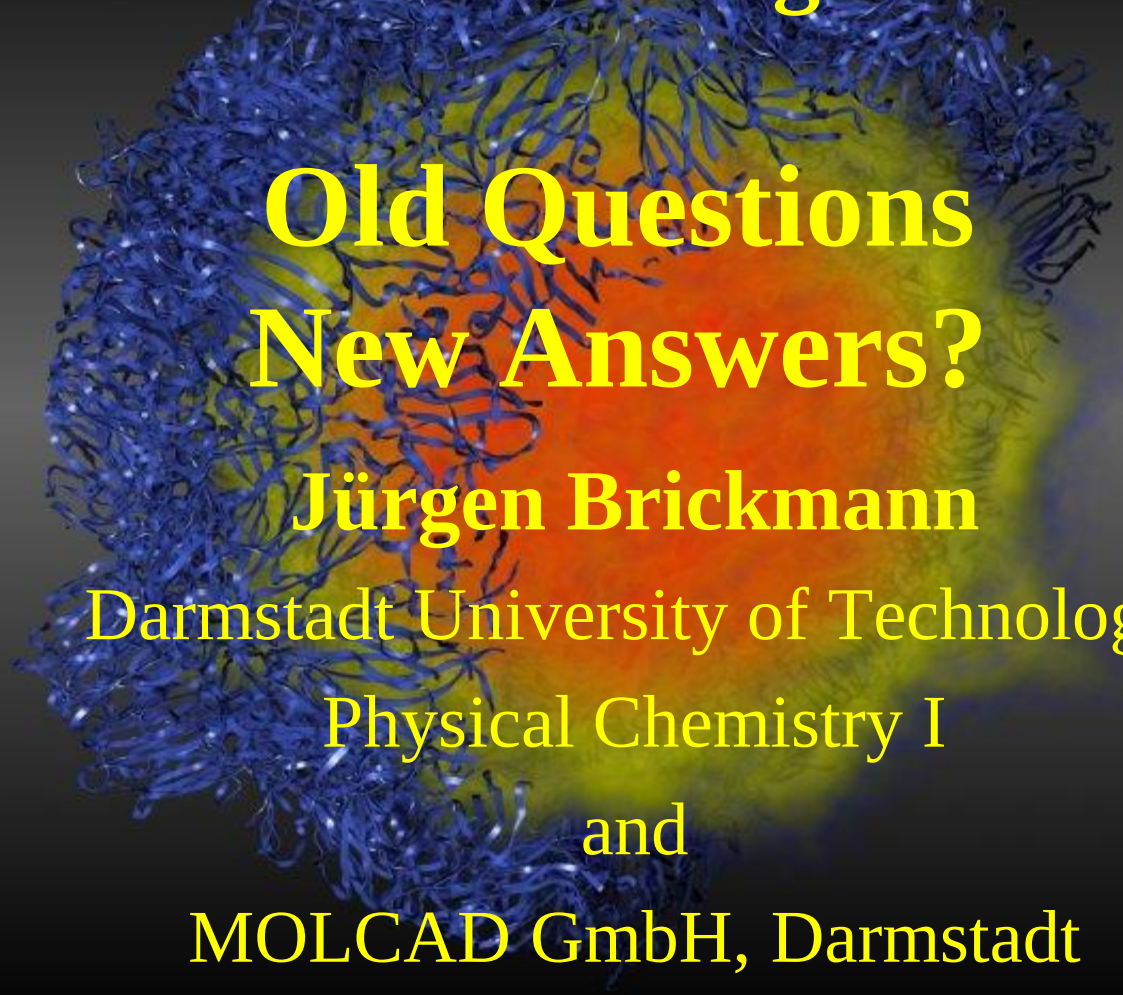


ERLANGEN 2011

25 Years
Molecular Modelling Workshop



Old Questions
New Answers?

Jürgen Brickmann

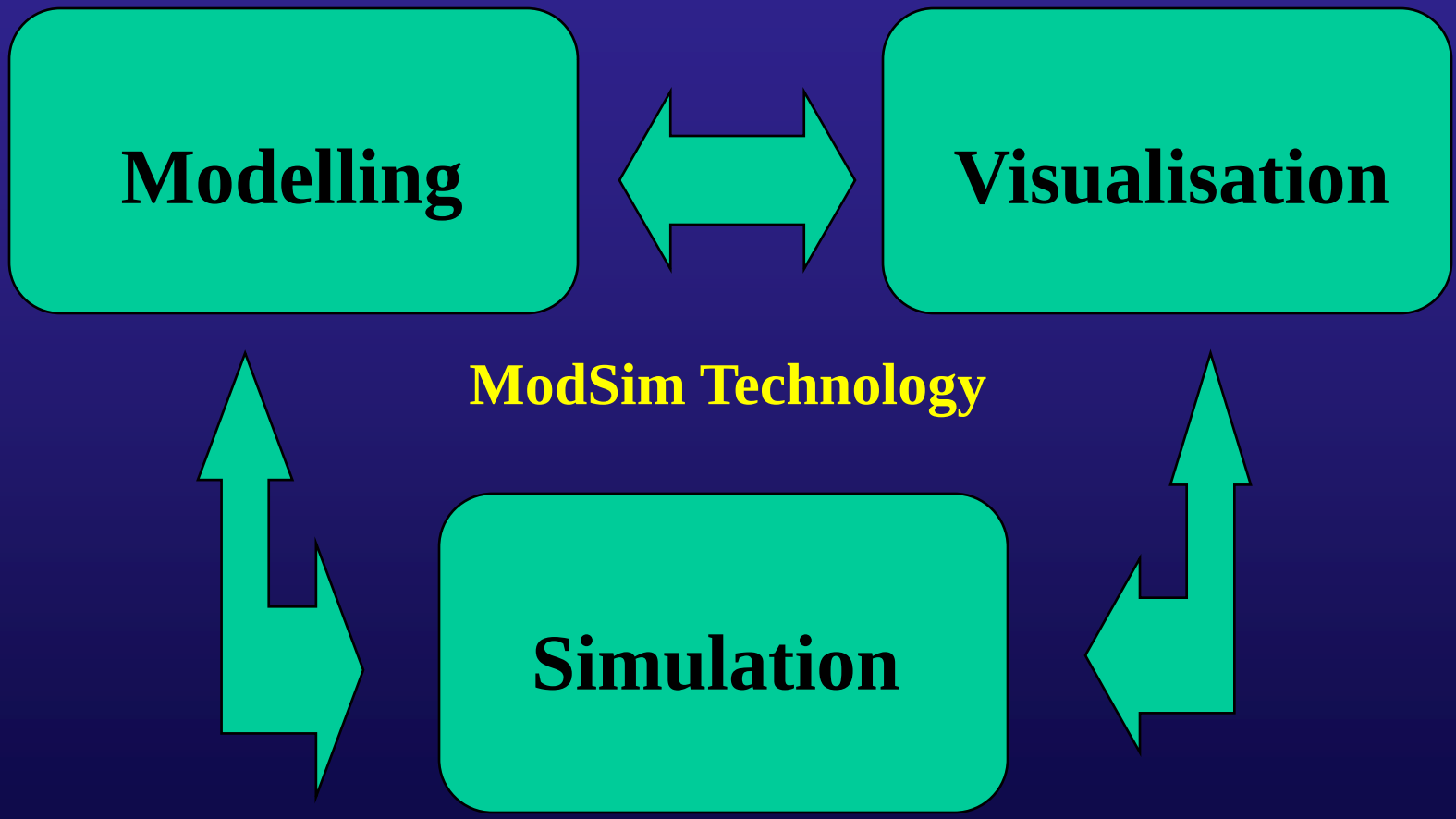
Darmstadt University of Technology

Physical Chemistry I

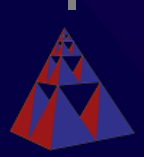
and

MOLCAD GmbH, Darmstadt

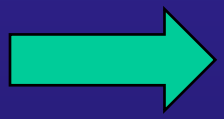
Modelling and Simulation



ModSim Technology in Molecular Science



ModSim Technology in Molecular Science



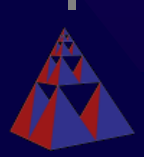
Materials Research

ModSim Technology in Molecular Science

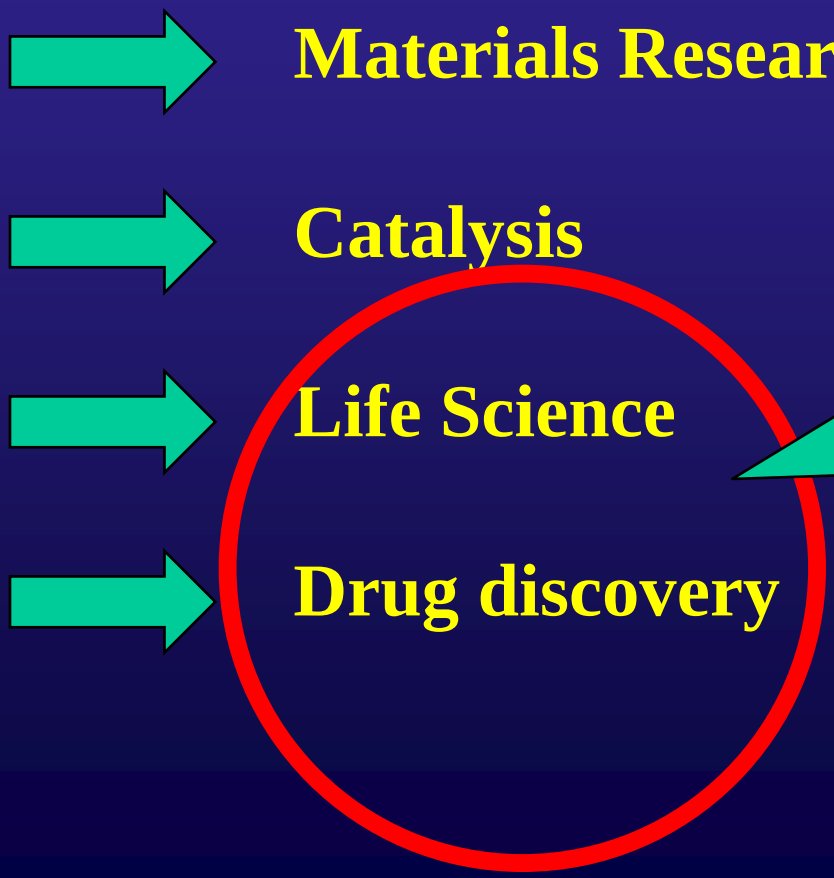
- Materials Research
- Catalysis

ModSim Technology in Molecular Science

- Materials Research
- Catalysis
- Life Science



ModSim Technology in Molecular Science



Focus of most of the Molecular Modelling Workshops since the beginning in 1987

The questions from the drug discovery community

From Industry:
How can computer aided methods be effectively used in order to reduce the effort for the developments of new drugs?

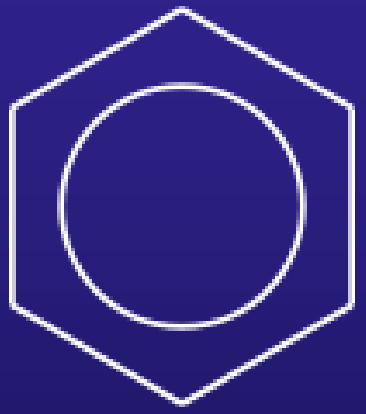
From Academia:
How can the interaction of a potential drug molecule with a receptor site (part of a protein) be adequately modelled? How can this interaction be quantified?

From both:
How can computer generated molecular scenarios be visualized in order to generate insight?

More general:
Can computers help to design new drugs against known deseases?

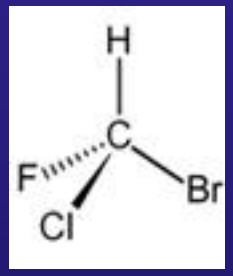
Molecular Modeling – Historical View

1859 Kekulé s Dream

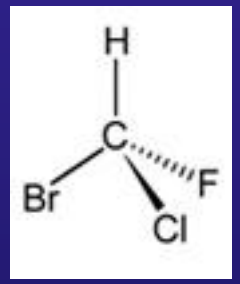


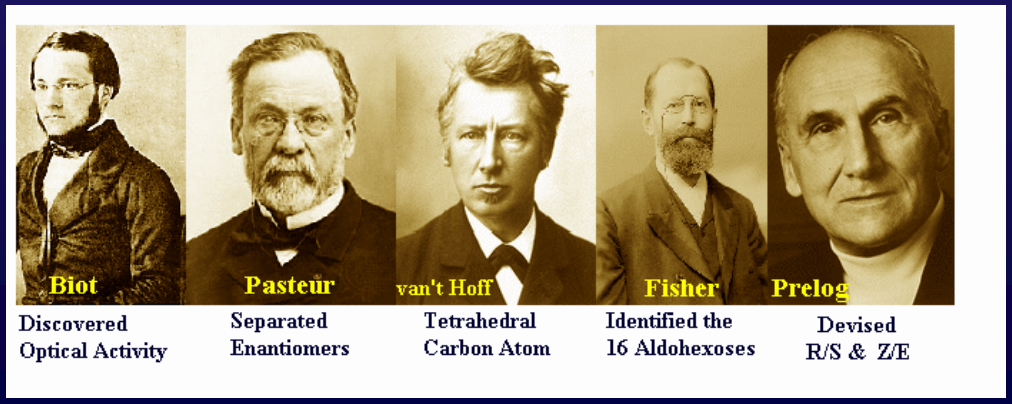
Molecular Modeling – Historical View

Around 1900 Stereochemistry



The part of chemistry that deals with structure in three dimensions is called stereochemistry. One aspect of stereochemistry is stereoisomers: same chemical formula but differ in the way atoms oriented in space.



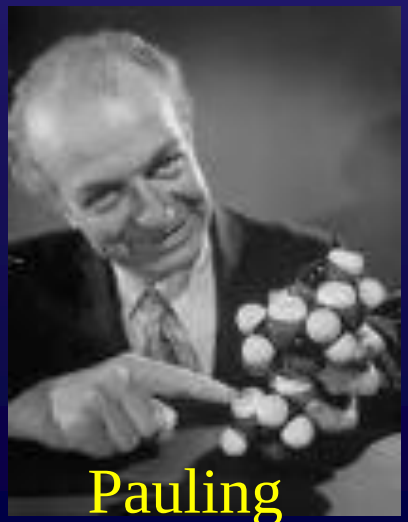


Molecular Modeling – Historical View

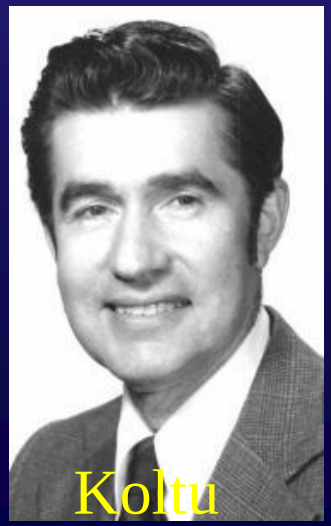
1953 CPK- models

Space-filling models represent the atoms as spheres whose radii are proportional to the atom's van der Waals radius. The best known of this type of model is the Corey-Pauling-Koltun (CPK) model. The original models of Corey and Pauling (1953) were made of hard wood

Corey

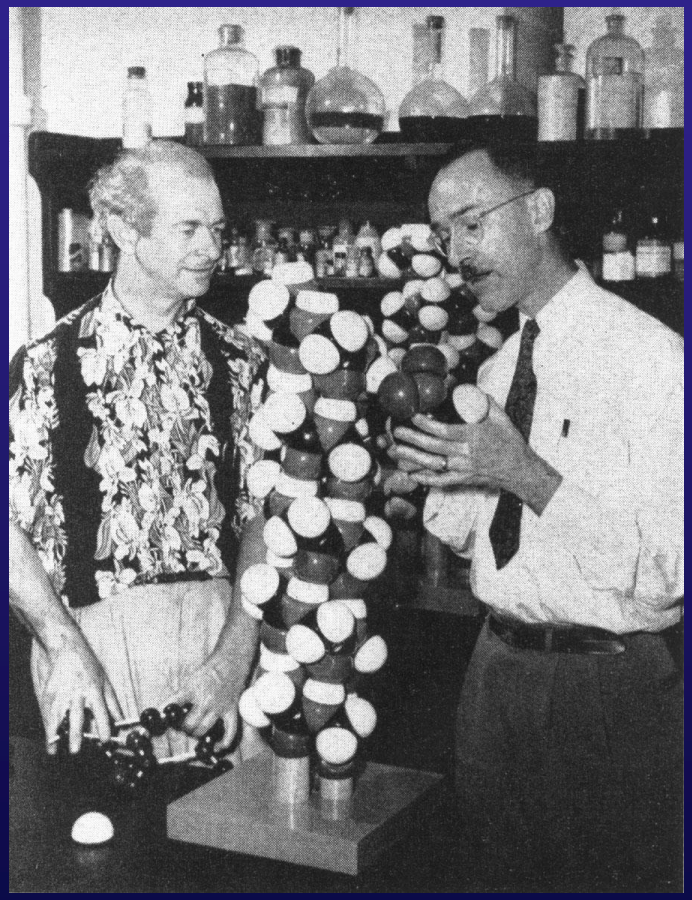


Pauling



Koltu

Molecular Modeling – Historical View
Physical Models (late fifties)



Pauling and Corey with a protein model

Kendrew with a protein model generated on the basis of x-ray studies

Hard work for scientists and modellers

Molecular Modeling – Historical View

1966: Molecular Graphics (MG)
First computer generated molecular images

First example of MG: Display of a protein molecule (Project MAC) by Cyrus Levinthal and Robert Langridge

1974

The Evans & Sutherland

PICTURE SYSTEM

The interactive, dynamic, 3-D line-drawing system.

PERSPECTIVE

Build models and display views of true three-dimensional objects.

DYNAMICS

Rotate, tumble or translate any object smoothly.

ZOOMING

Smooth, quick transition to any scale.

CONVENIENCE

Your choice of coordinates and language.

INTERACTION

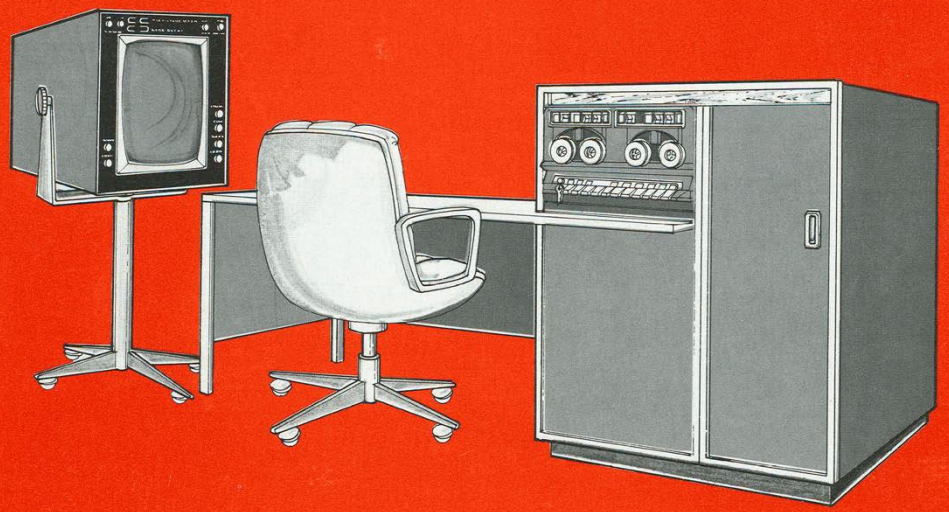
Change, test or manipulate as you wish.

QUALITY

Sharp pictures at all times.

VALUE/SERVICE/SUPPORT

Now anyone can afford the very best.



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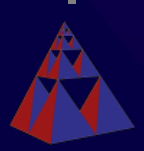
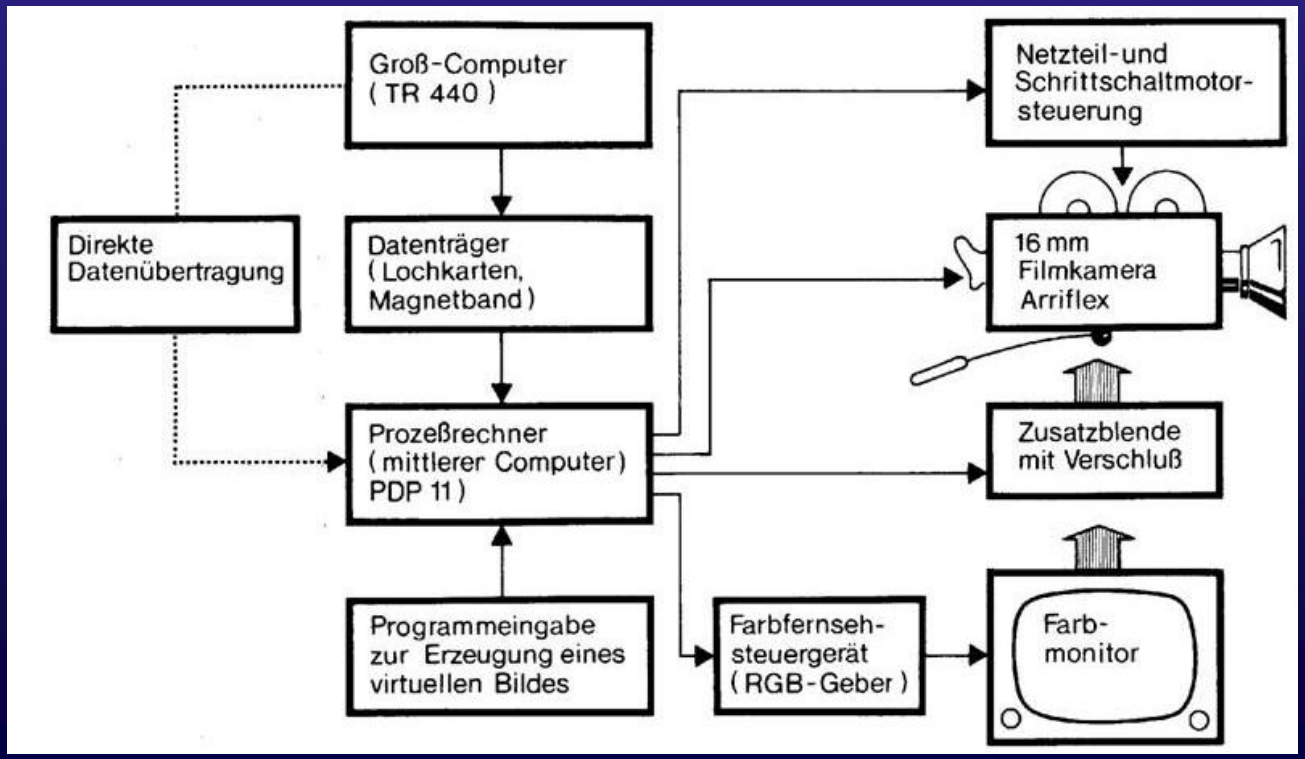


Molecular Modeling – Historical View

1974-76: J. Brickmann
Development of Raster Graphics Hardware
Project SIDCEP
(Simulation und Darstellung chemischer Elementarprozesse)



Molecular Modeling – Historical View

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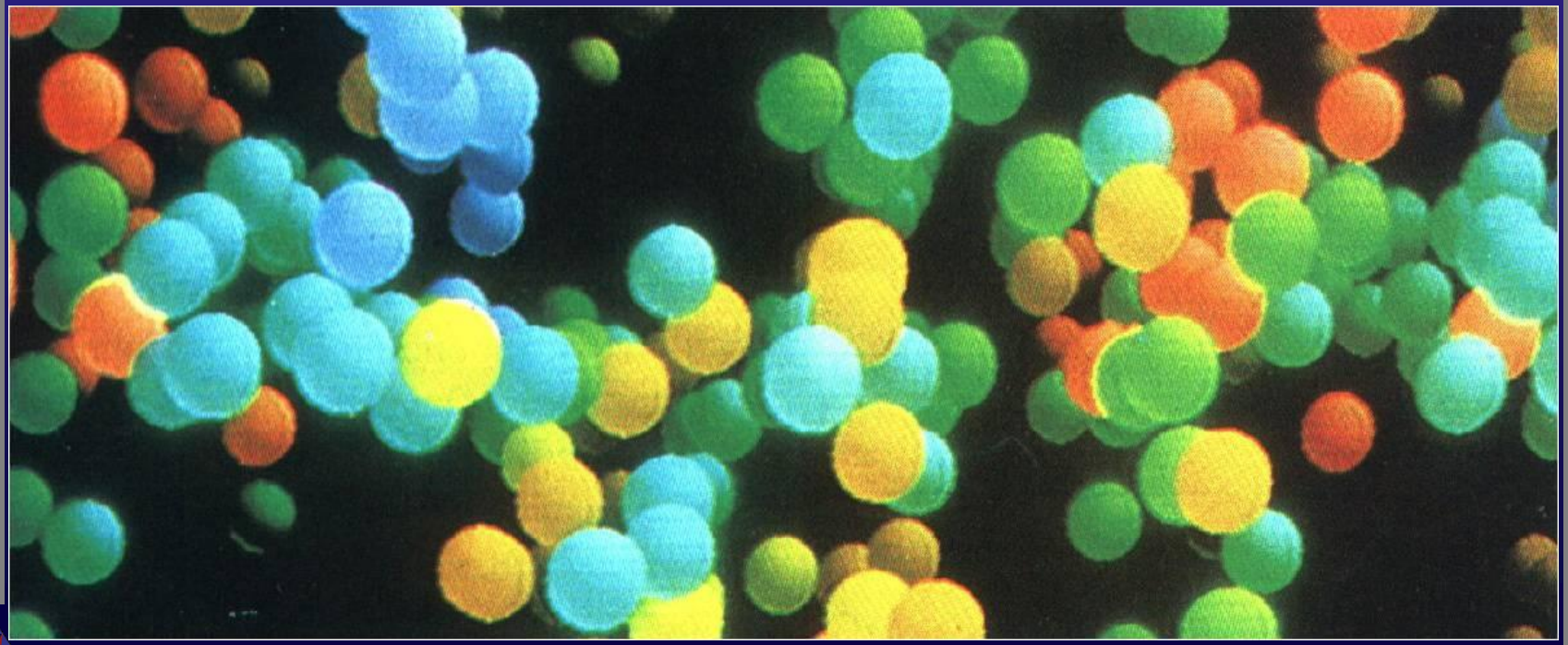
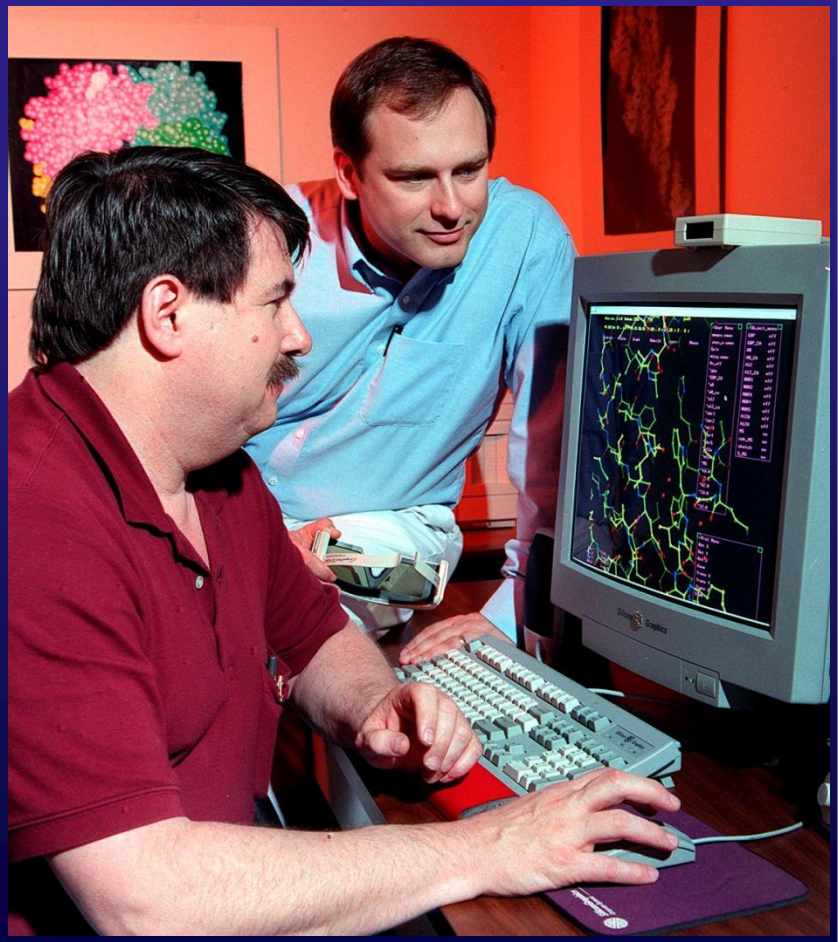


Molecular Modeling – Historical View

1982 Silicon Graphics Workstations- The victory of raster Graphics

Dr. James H. Clark left his position as an electrical engineering associate professor at Stanford University to found SGI in 1982 along with a group of seven graduate students and research staff from Stanford



Molecular Modeling – Historical View

From Molecular Graphics to Molecular Modelling

Wikipedia:

By about 1980 many laboratories both in academia and industry had recognized the power of the computer to analyse and predict the properties of molecules, especially in materials science and the pharmaceutical industry. The discipline was often called "molecular graphics" and in 1982 a group of academics and industrialists in the UK set up the Molecular Graphics Society (MGS). Initially much of the technology concentrated either on high-performance 3D graphics, including interactive rotation or 3D rendering of atoms as spheres. During the 1980s a number of programs for calculating molecular properties became available and the term "molecular graphics" often included these.

As a result the MGS has now changed its name to the Molecular Graphics and Modelling Society (MGMS).

Back to the initial questions

How can computer generated molecular scenarios be visualized in order to generate insight?

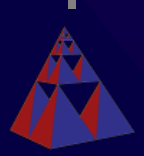
How can the interaction of a potential drug molecule with a receptor site (part of a protein) be adequately modelled? How can this interaction be quantified?

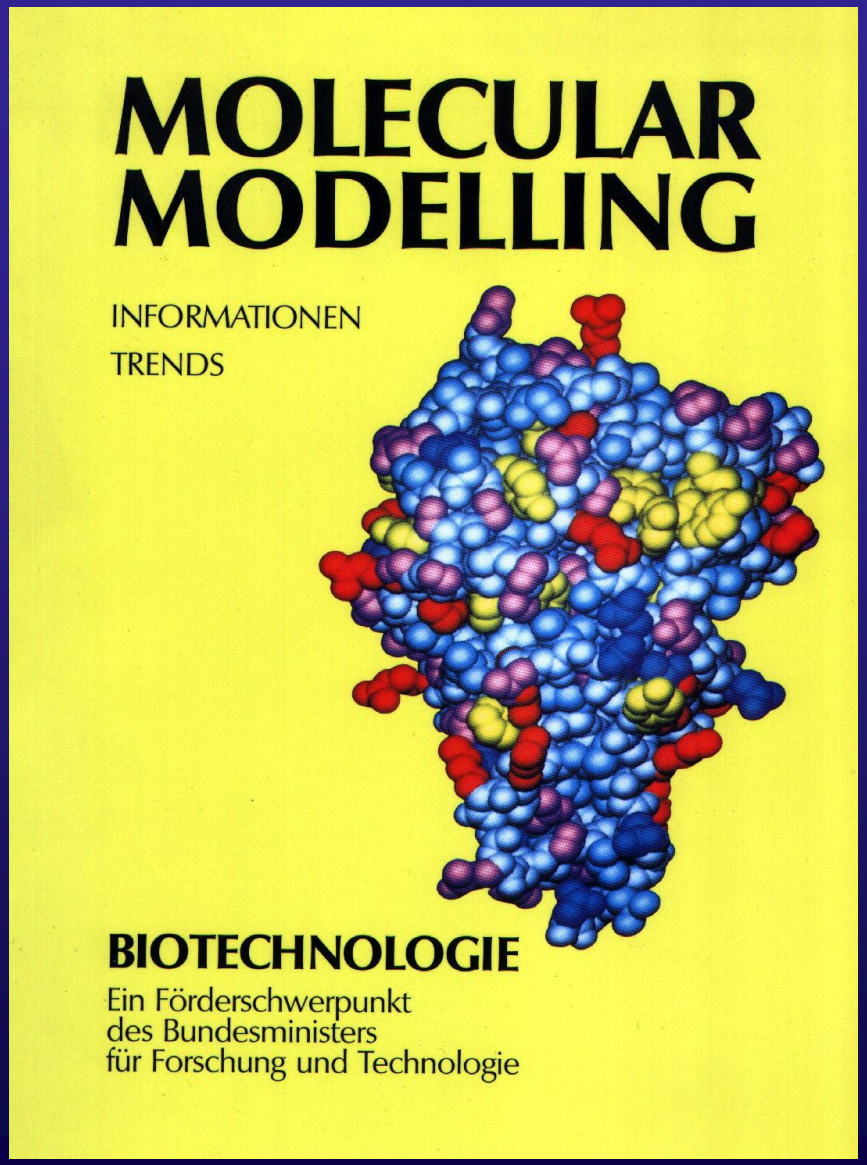
How can computer aided methods be effectively used in order to reduce the effort for the developments of new drugs?

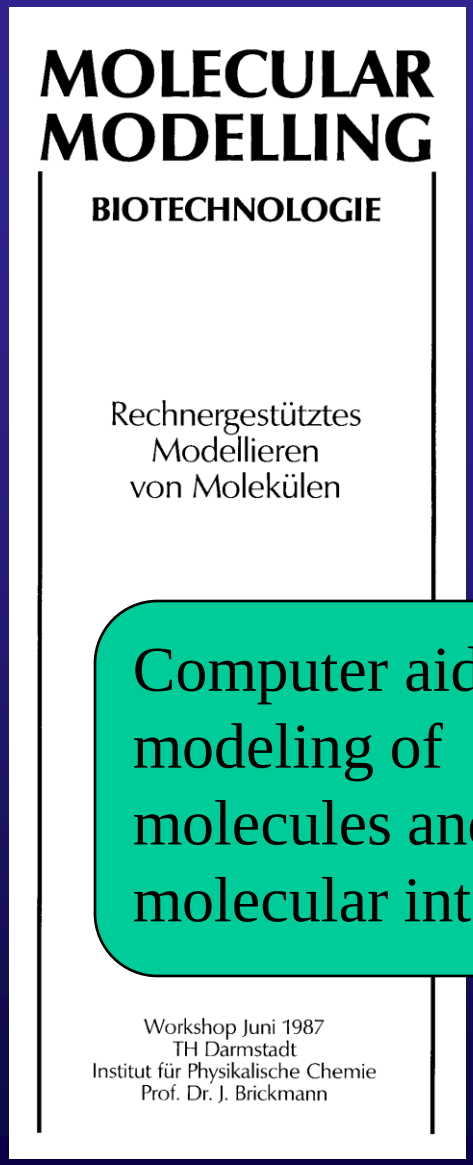
Can computers help to design new drugs against known deseases?

The questions from the drug discovery community

The 1987 anwers can be estimated by looking on the papers represented at the first molecular modelling workshop, Darmstadt 1987, published in 1988 by the German Ministry of Science and Technology







Darmstadt 1987

Computer aided modeling of molecules and molecular interactions

The first Molecular Modelling Workshop

MOLECULAR MODELLING

"Black box" oder transparente Methode

von

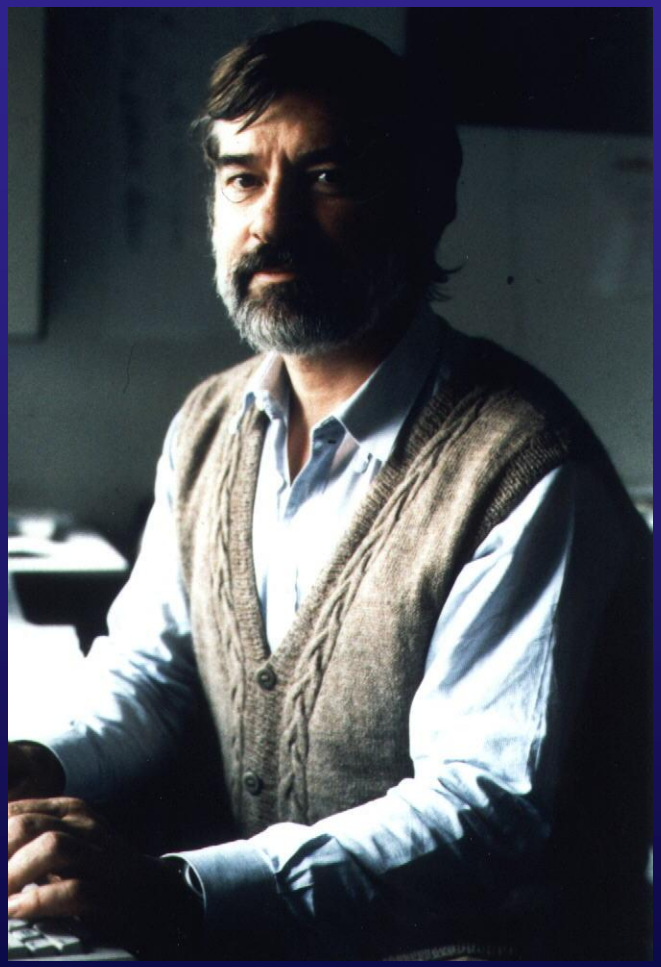
Jürgen Brickmann

Institut für Physikalische Chemie

Technische Hochschule Darmstadt

Petersenstraße 20, D-6100 Darmstadt

MOLECULAR MODELING
„Black box“
or transparent method

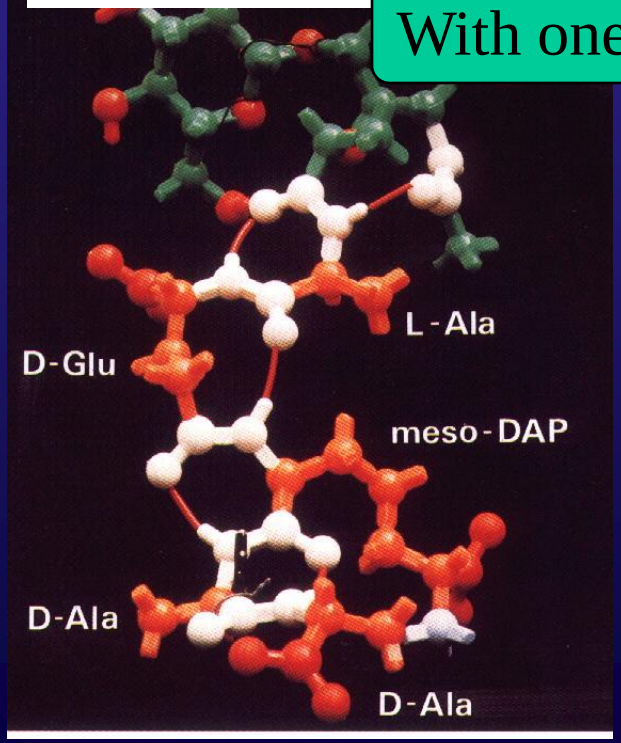


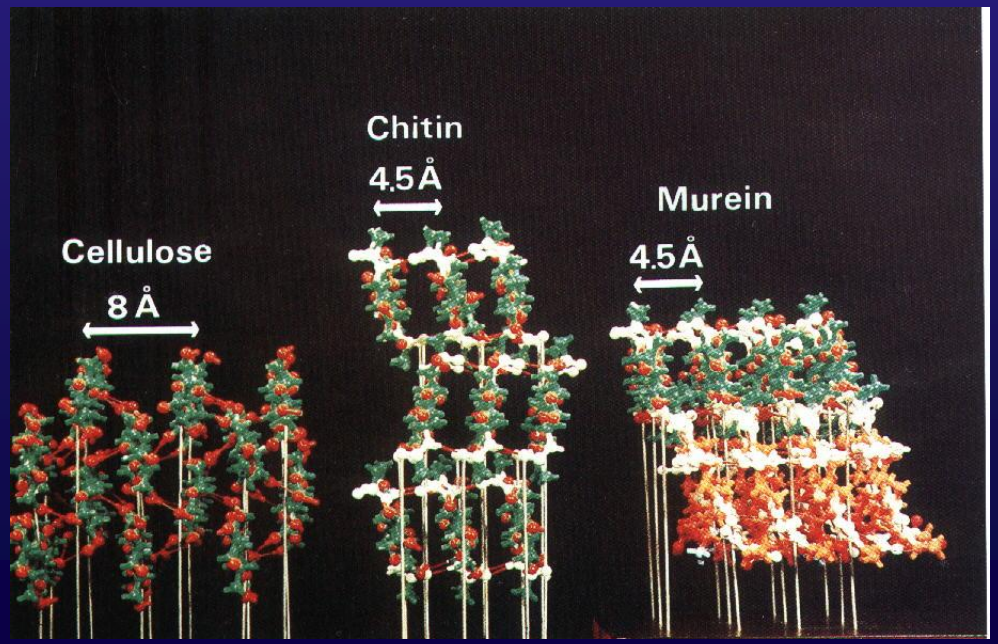
Ein dreidimensionales, atomares Modell der Mureinschicht von Bakterienzellwänden

Helmut Formanek

Botanisches Institut der Universität München, Menzinger Straße 67,

With one leg in the CPK world





MOLECULAR GRAPHICS-UNTERSUCHUNGEN ZUM WIRKUNGSMECHANISMUS VON CALCIUMANTAGONISTEN UND CALCIUMAGONISTEN DER 1,4-DIHYDROPYRIDINREIHE (*)

H.-D. Höltje, S. Marrer
Pharmazeutisches Institut, Freie Universität Berlin

Visualisation of molecular properties and molecular interactions

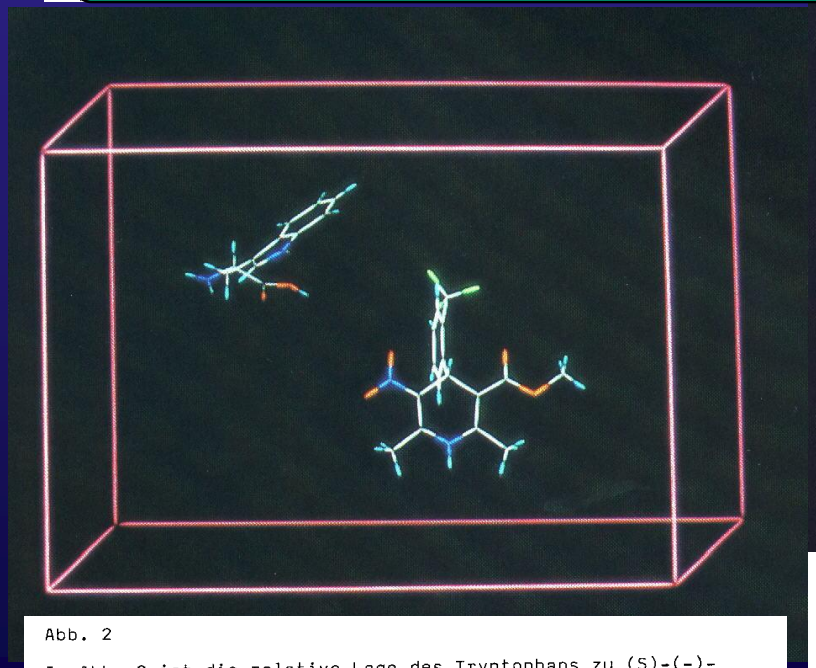


Abb. 2

In Abb. 2 ist die relative Lage des Tryptophans zu (S)-(-)-BAY K 8644 als ein Beispiel der untersuchten Komplexe dargestellt.

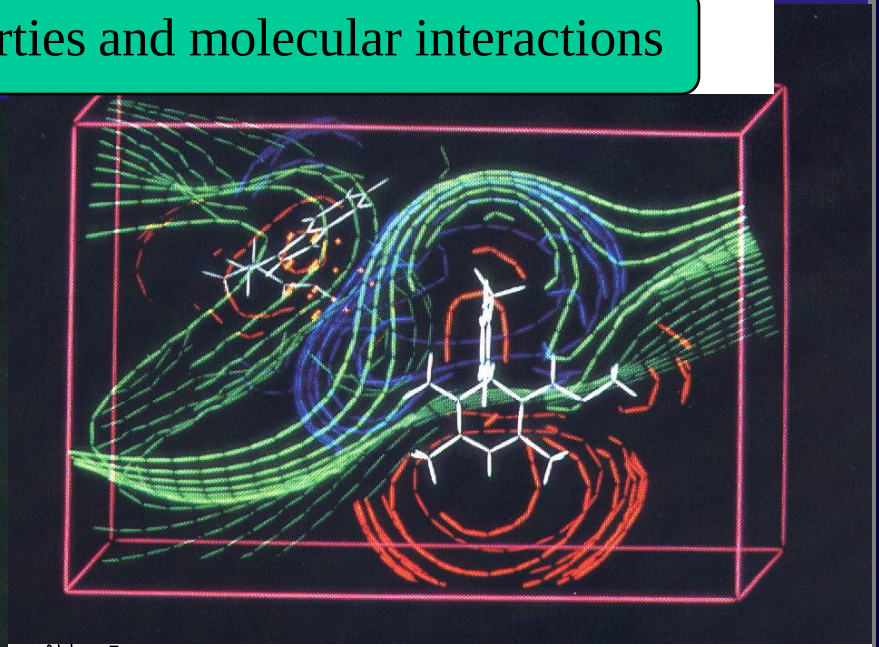


Abb. 3

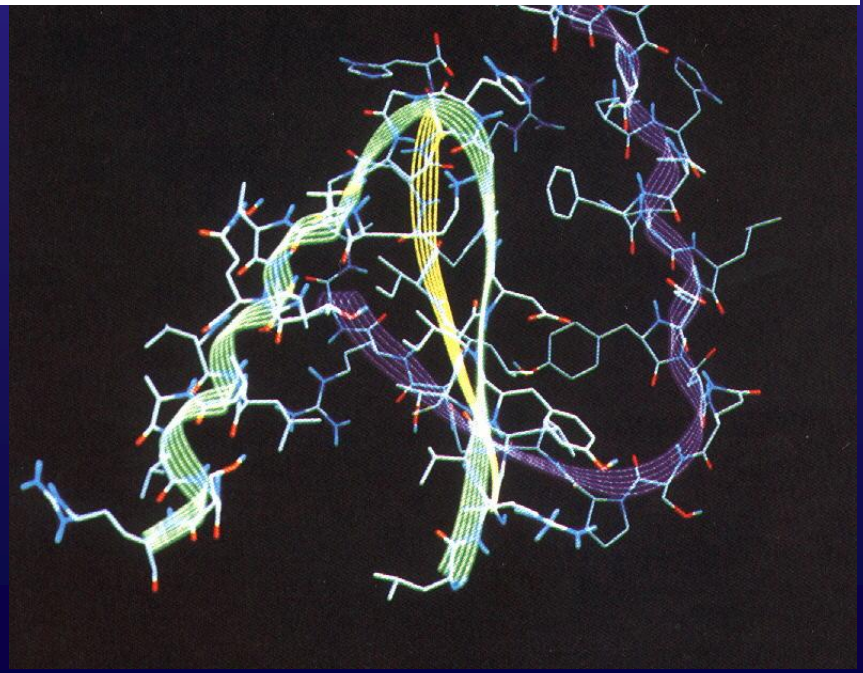
Elektrostatische Isopotentiallinien für den Tryptophan-(S)-(-)-BAY K 8644 Komplex. Konturierungsniveaus: rot, +12 kJ/mol; blau, -12 kJ/mol; grün, 0 kJ/mol. Orange Kreuze zeigen das Raumsegment, wo Potentialunterschiede zwischen Agonisten und Antagonisten vorliegen.

Versuche zur Computergraphik gestützten Konstruktion von active site Partialstrukturen in Kinasen.

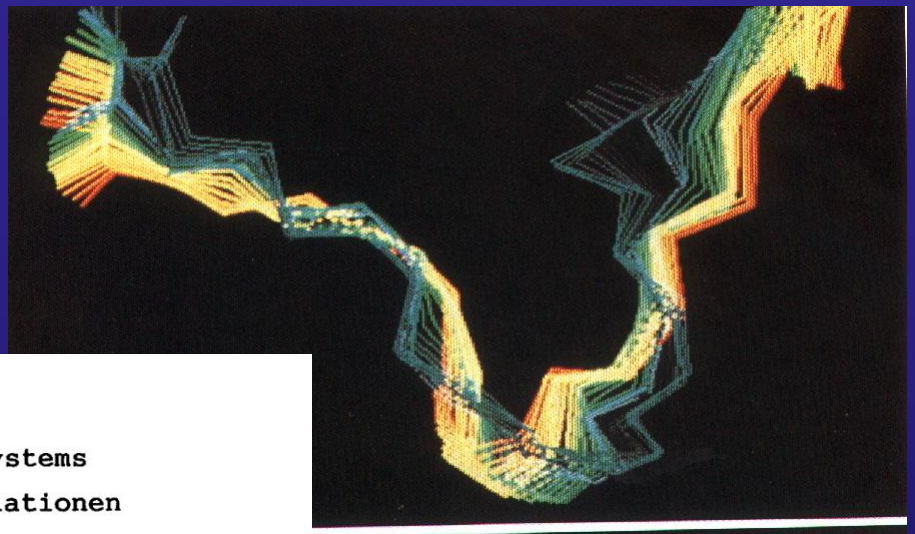
Gerd Folkers

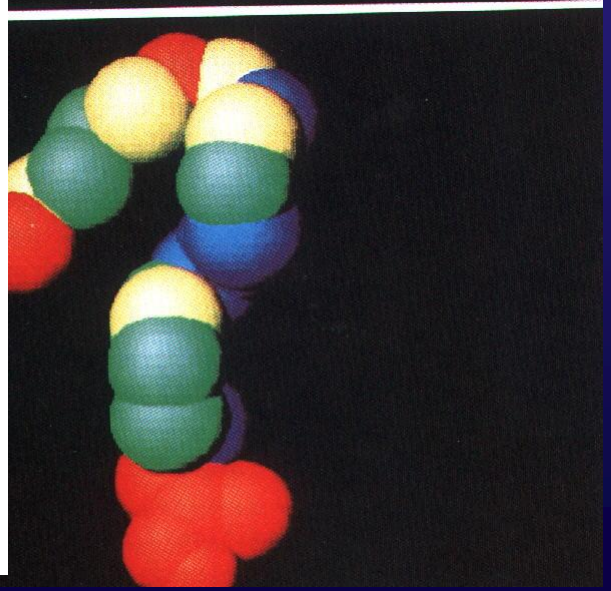
Pharmazeutisches Institut der Universität, Auf der Morgenstelle 8, D-7400 Tübingen

Computer aided construction of active site partial structures in kinases



Computer graphical method for the interpretation of molecular dynamics simulations





Entwicklung eines Auswertesystems
für die Moleküldynamik Simulationen

P. Krüger, W. Straßburger*, A. Szameit, A. Grötzinger, J. Hahnen, A. Wollmer.

Lehrgebiet Struktur und Funktion der Proteine
Abteilung Physiologische Chemie
Rheinisch-Westfälische Technische Hochschule Aachen
5100 Aachen

*)Grünenthal GmbH
Forschungszentrum
51oo Aachen-Eilendorf

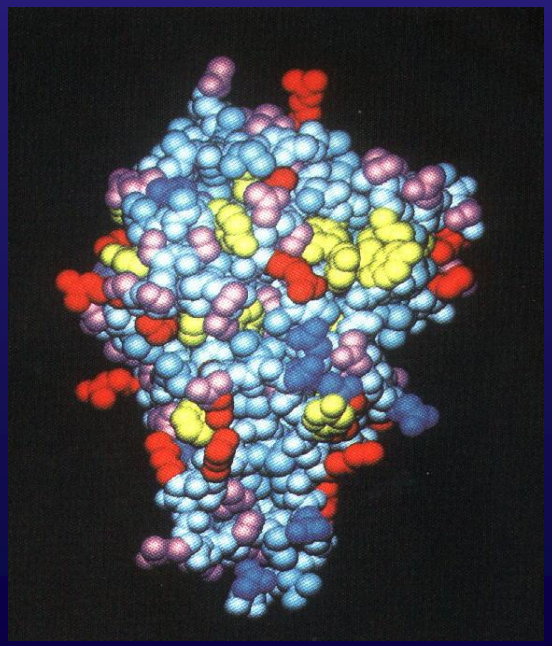
CAPD

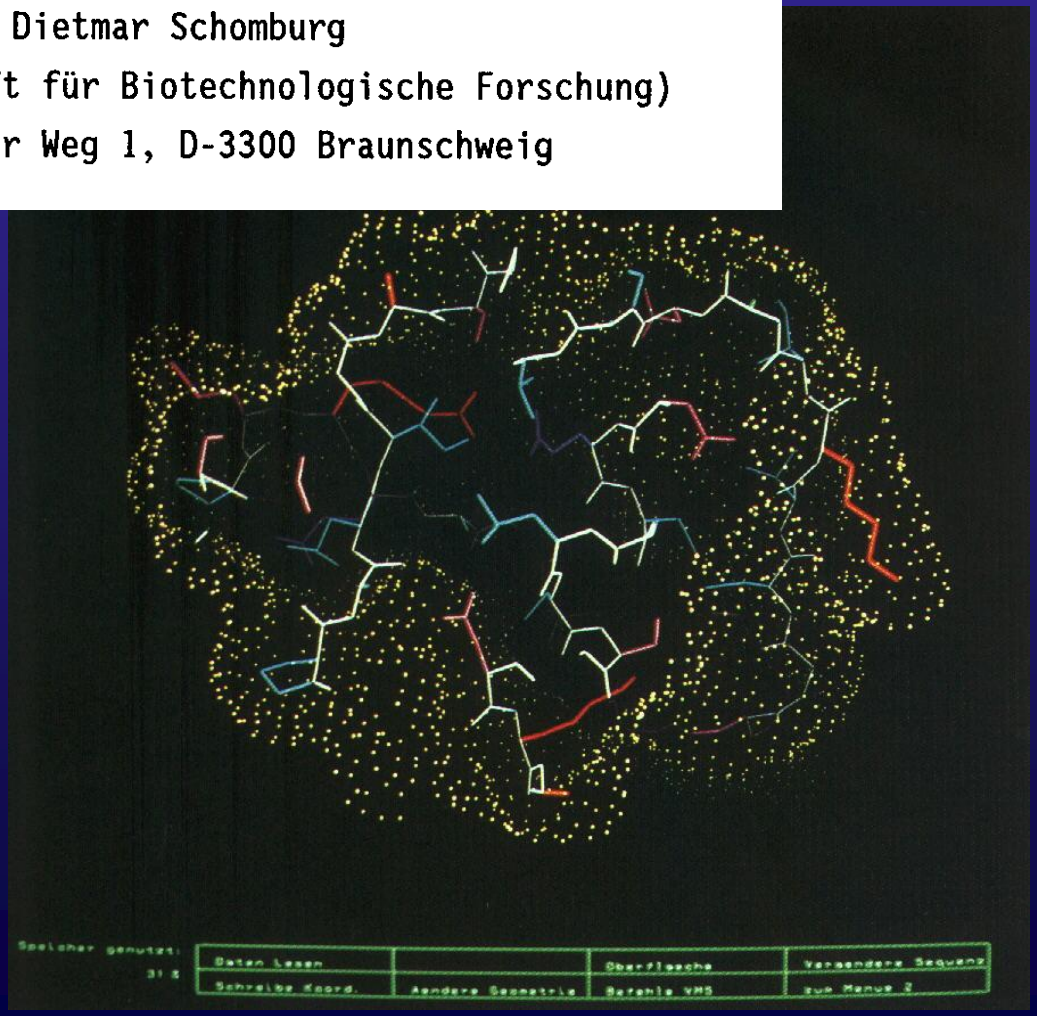
Methodik des Computer Aided Protein Design

Dietmar Schomburg

GBF (Gesellschaft für Biotechnologische Forschung)

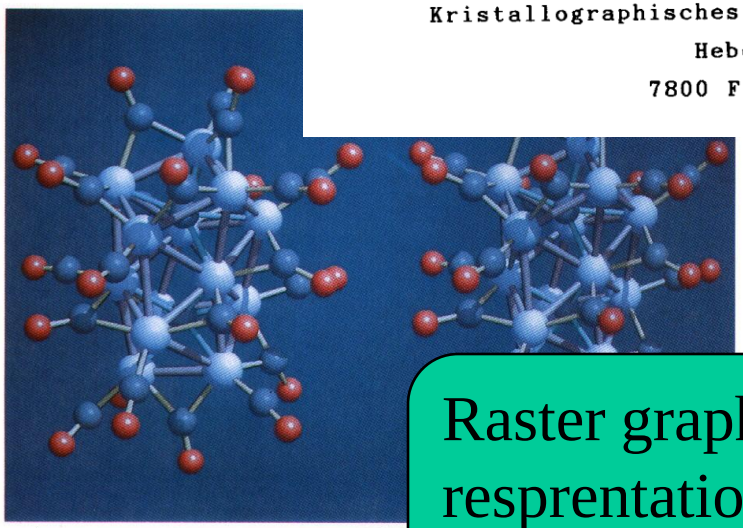
Mascheroder Weg 1, D-3300 Braunschweig

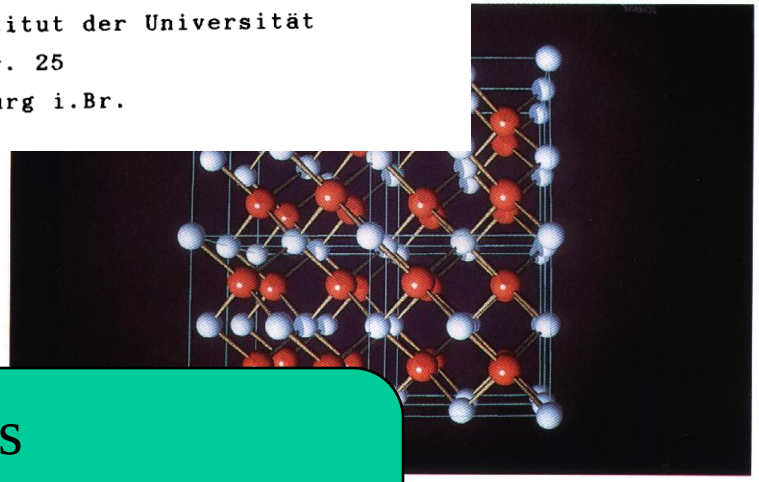




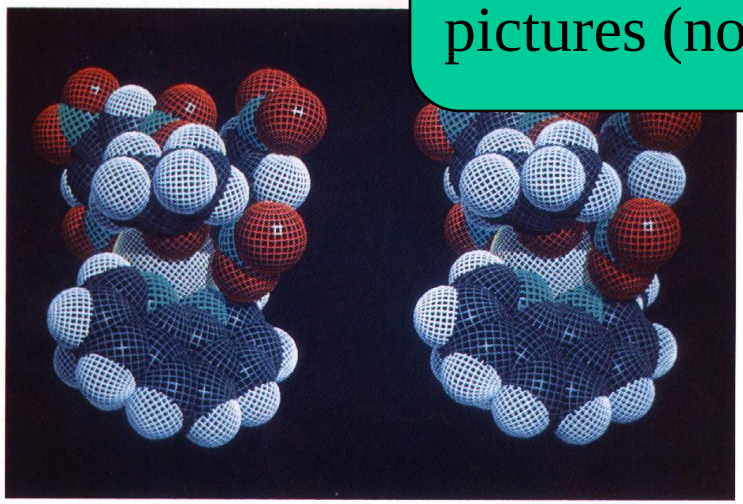
SCHAKAL86, ein FORTRAN-Programm zur grafischen Darstellung von Molekül- und Festkörpermodellen

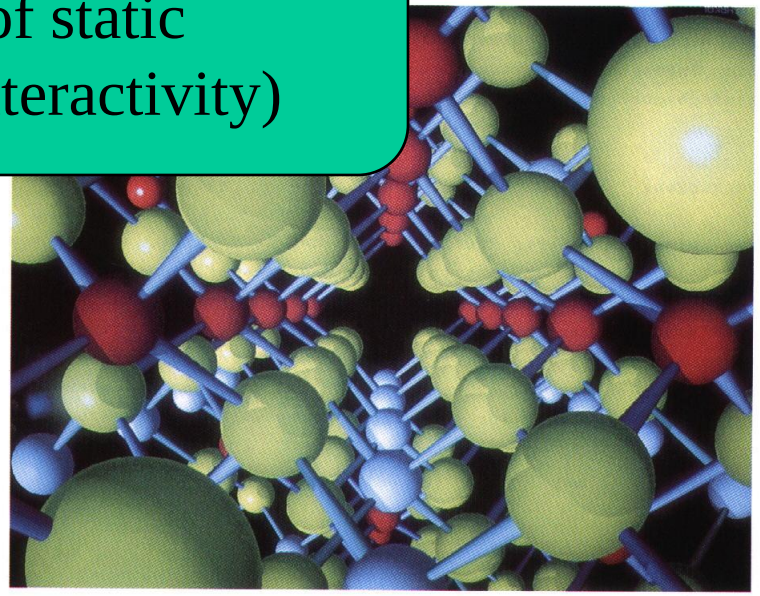
Egbert Keller
Kristallographisches Institut der Universität
Hebelstr. 25
7800 Freiburg i.Br.





Raster graphics
resprentation of static
pictures (no interactivity)





C.W. von der Lieth, R.E. Carter, T. Liljefors: SIMulate PEPtid

SIMulate PEPtid – ein computergrafisches Interface zur Konstruktion, Wiedergabe und Berechnung von Oligopeptiden

C W v d Lieth(*), R E Carter(#), Tommy Liljefors(#)

(#) University of Lund, Chemical Center, Organic Chemistry 2 and 3
P.O.B 124 S–2210 Lund Sweden

(*) Deutsches Krebsforschungszentrum (ZAGS) Im Neuenheimer Feld 280
6900 Heidelberg West Germany

Implementierung

The interface problems

Die Programme sind (Ausnahme DISGEO: spezielles VAX–PASCAL) in FORTRAN 77 auf einer VAX 11/780 unter VMS lauffähig (Ausnahme: MUMOD vektorisiertes FORTRAN Programm auf einer IBM 3090 mit Vektor–Feature). Der grafische Teil benutzt PLOT–10 kompatible Terminals (VISUAL 500 Serie), die selektives Löschen von Teilen eines Moleküls und Aufteilung des Bildschirms in einen alphanumerischen und einen grafischen Teil ermöglichen.

Von der Vektorgraphik am Zentralrechner zur Rastergraphik auf einer Workstation - Eine vergleichende Gegenüberstellung nach der Übertragung eines Software-Paketes

J. Reichelt

GBF (Gesellschaft für Biotechnologische Forschung mbH)

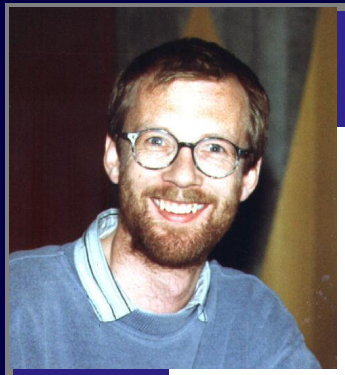
Mascheroder Weg 1, D-3300 Braunschweig

First steps from vector graphics technology towards raster graphics workstations

…and other problems of „super computers“

Die Anwendung von Vektorrechnern und anderer sehr leistungs-fähiger Rechnersysteme.

Philippe Bopp
Institut für Physikalische Chemie
Technische Hochschule Darmstadt
Petersenstrasse 20, D-6100 Darmstadt



Workstation und PC - gemeinsamer Einsatz im Molecular Modelling

Dipl.-Ing. Michael Waldherr - Teschner
Technische Hochschule Darmstadt
Institut für Physikalische Chemie
Petersenstraße 20 6100 Darmstadt

and the origen of MOLCAD

Anhand des an der TH-Darmstadt entwickelten Programms MOLCAD soll die gemeinsame Verwendung von PC und Workstation im Bereich des Molecular Modellings aufgezeigt werden. Wichtig dabei ist, daß für den Benutzer auf beiden Systemen die gleiche Benutzeroberfläche vorhanden ist, und daß die grundlegenden Operationenen die gleiche Funktionalität besitzen. Der PC soll dabei nicht die Workstation ersetzen, sondern wird in einem Gesamtkonzept als Low-End angesehen, das für wenig Geld eine breite Anwendung graphischer Methoden im Molecular Modelling bietet.

And what ist the situation today
The anwers from 2011

How can computer generated molecular scenarios be visualized in order to generate insight?

How can the interaction of a potential drug molecule with a receptor site (part of a protein) be adequately modelled? How can this interaction be quantified?

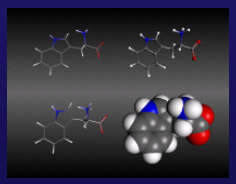
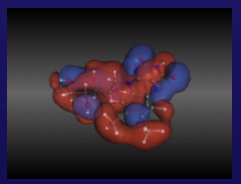
How can computer aided methods be effectively used in order to reduce the effort for the developments of new drugs?

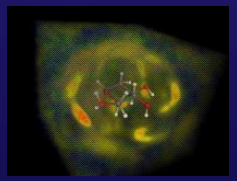
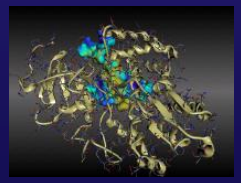
Can computers help to design new drugs against known deseases?

Back to the initial questions and answers from 2011

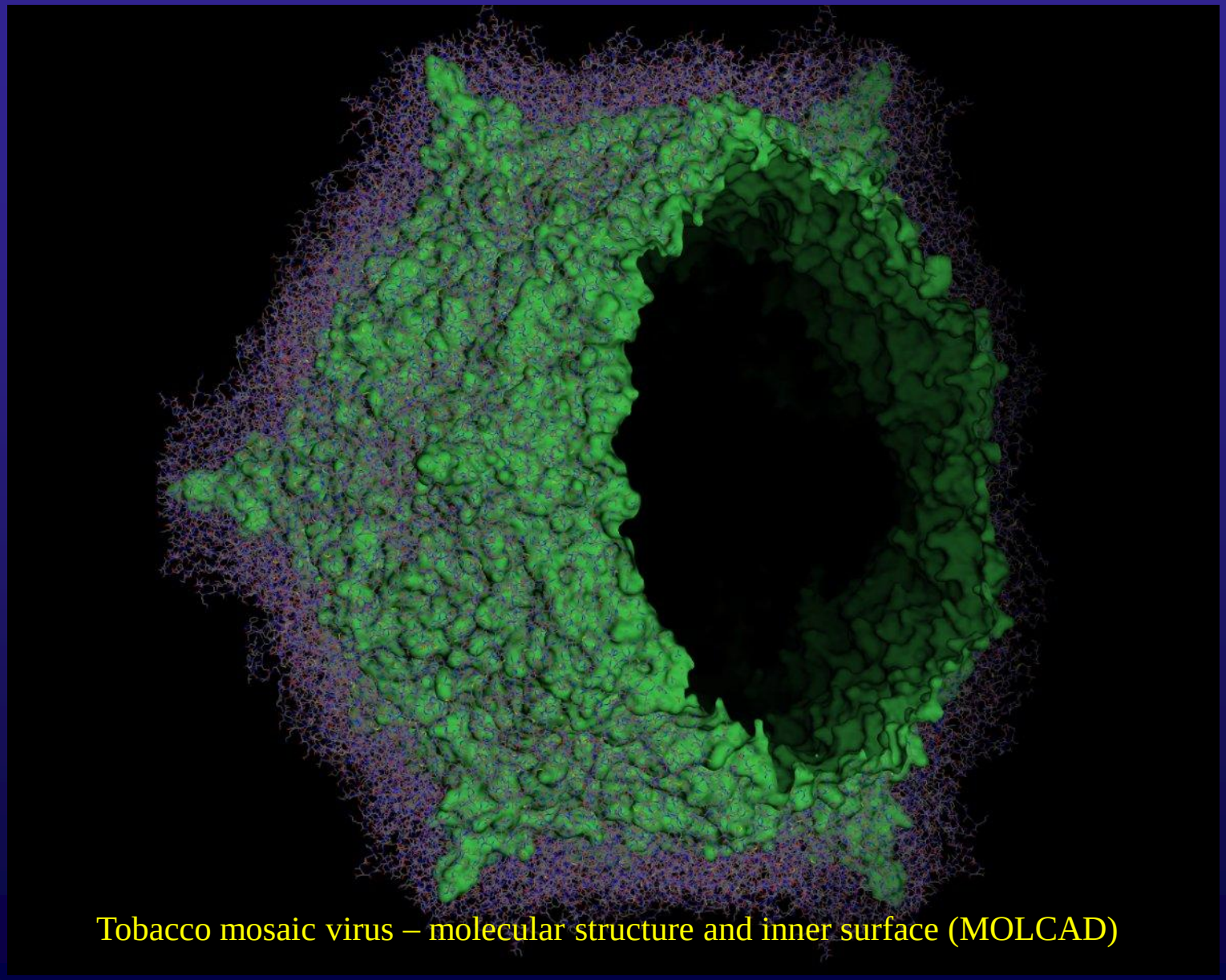
How can computer generated molecular scenarios be visualized in order to generate insight?

No problems!
Various tools are available
Example: MOLCAD

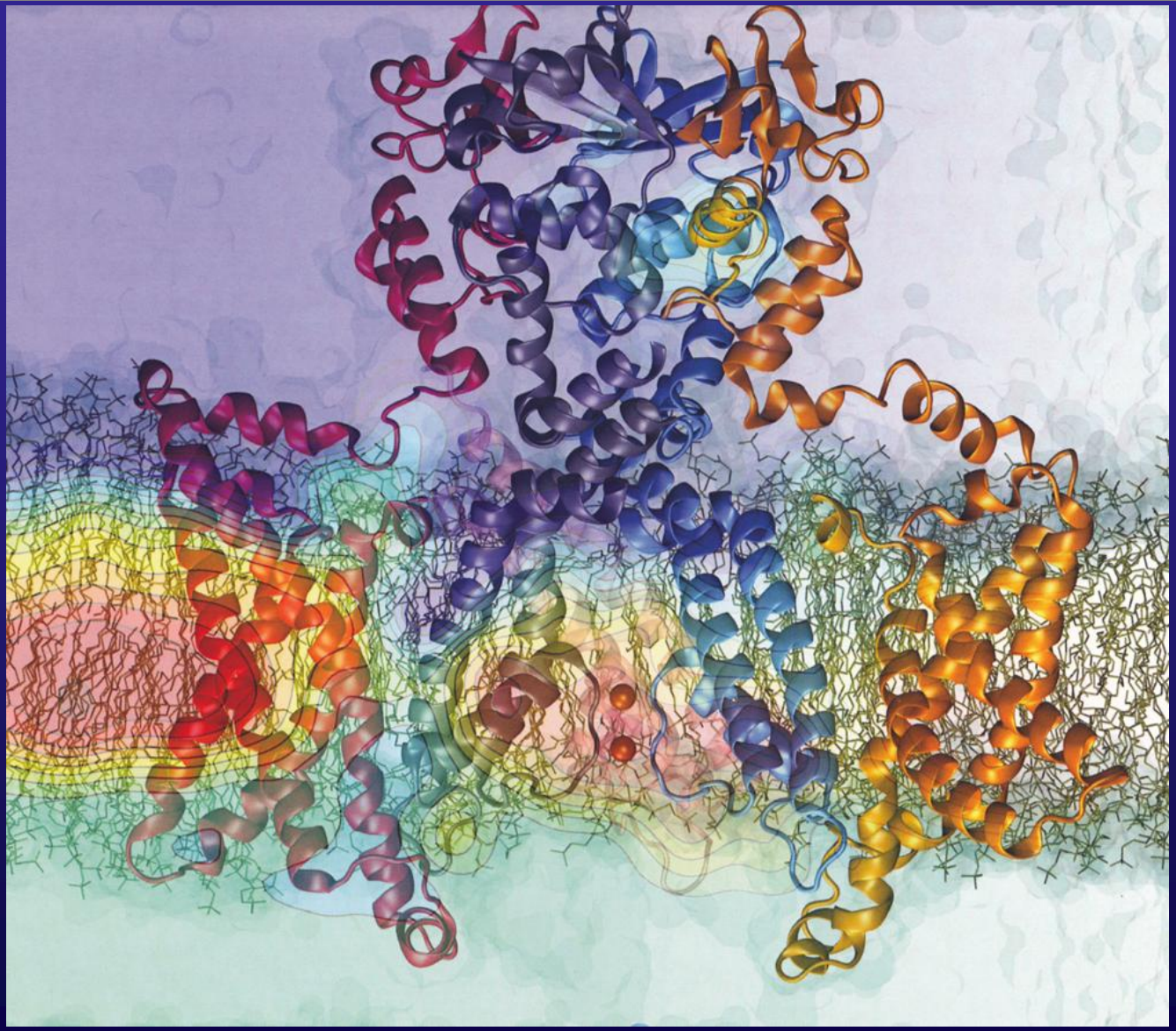



……and even more complex molecular aggregates:



Tobacco mosaic virus – molecular structure and inner surface (MOLCAD)



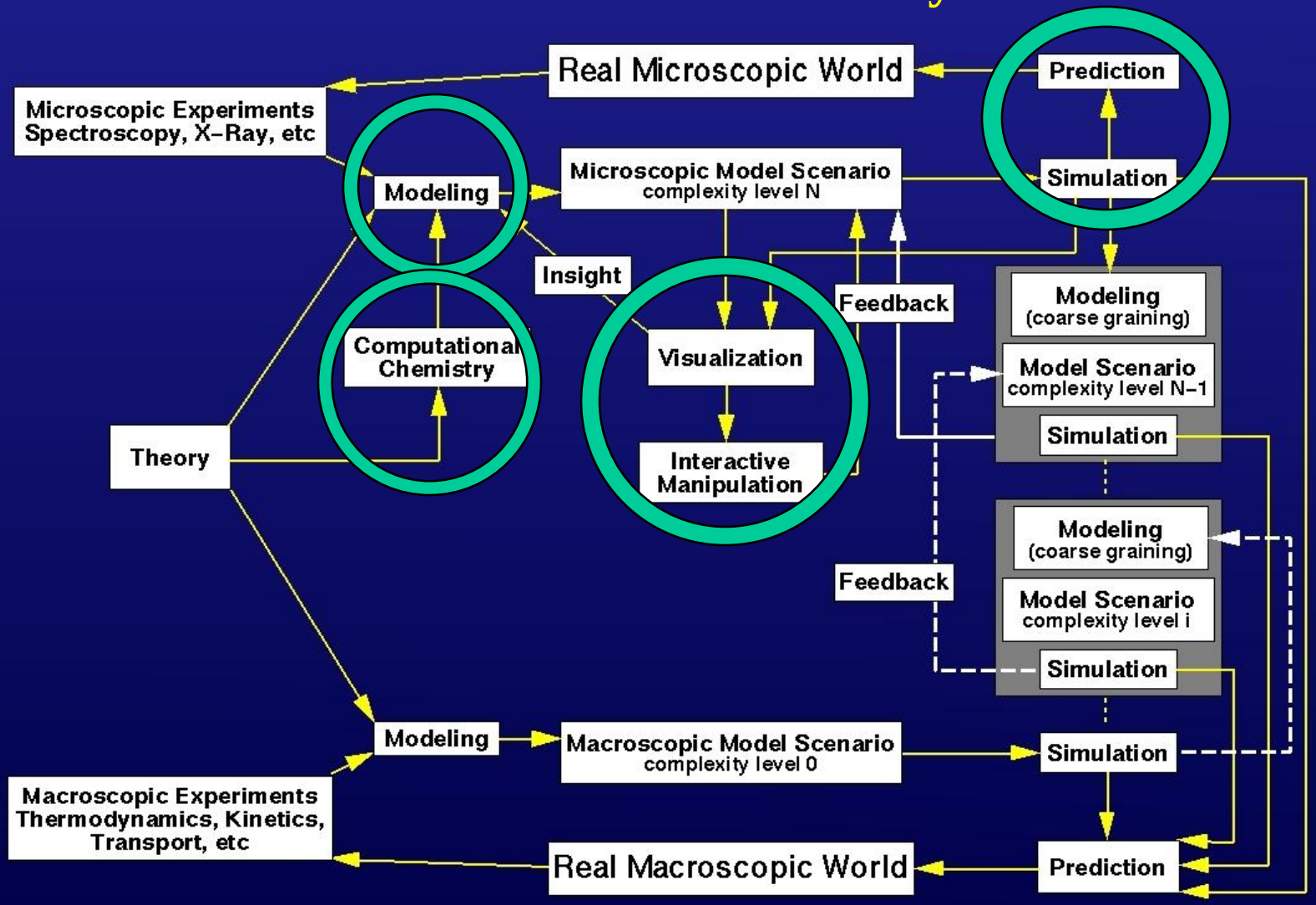
F. Khalili:Electrostatic potential of a voltage driven potassium channel.
Schulten calender 2011

And what ist the situation today
The anwers from 2011

How can the interaction of a potential drug molecule with a receptor site (part of a protein) be adequately modelled? How can this interaction be quantified?

1. **The computer capacity increased by five orders of magnitude (Moore´s law is still valid)**
2. **The quality and power of model scenarios substantially stepped foreward:**
   Quantum methods have been included
   Better force fields
   Enhanced simulation techniques
   Inclusion of solvent
   (ΔG values)

The 2011 fields of activity



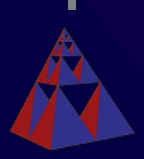
And what ist the situation today
The anwers from 2011

How can computer aided methods be effectively used in order to reduce the effort for the developments of new drugs?

The dramatic expansion of hardware- and in particular software technology has definitely contributed to the development of new drugs for those cases where the receptor is known.

Statistical methods cotributed significantly to the pre-selection of drug candidates. Details are not known to the public.

However, in many aspects one ist still at the beginning.



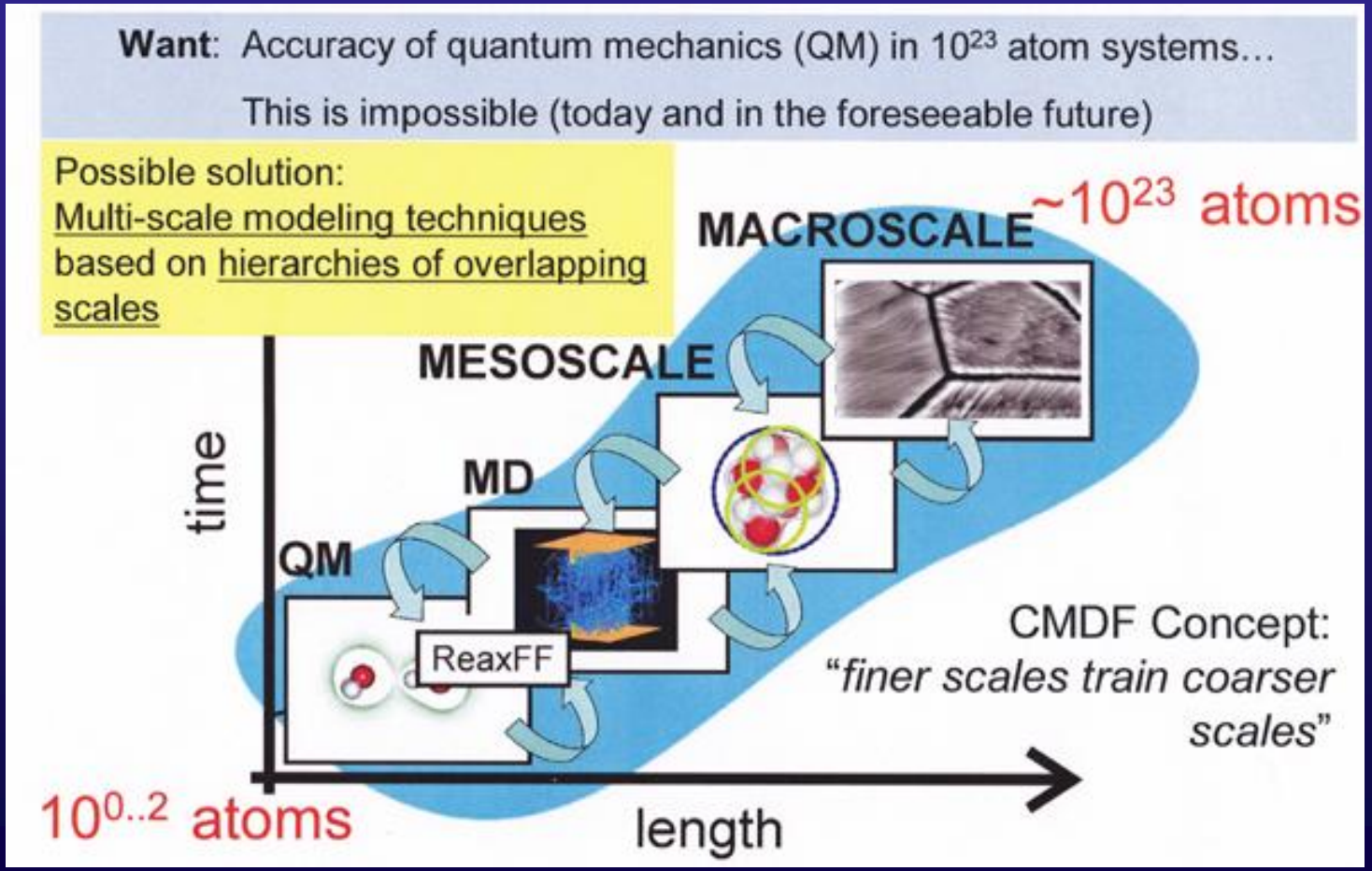
And what ist the situation today
The anwers from 2011

Can computers help to design new drugs against known deseases?

possibly Yes
but not with the
present
technology

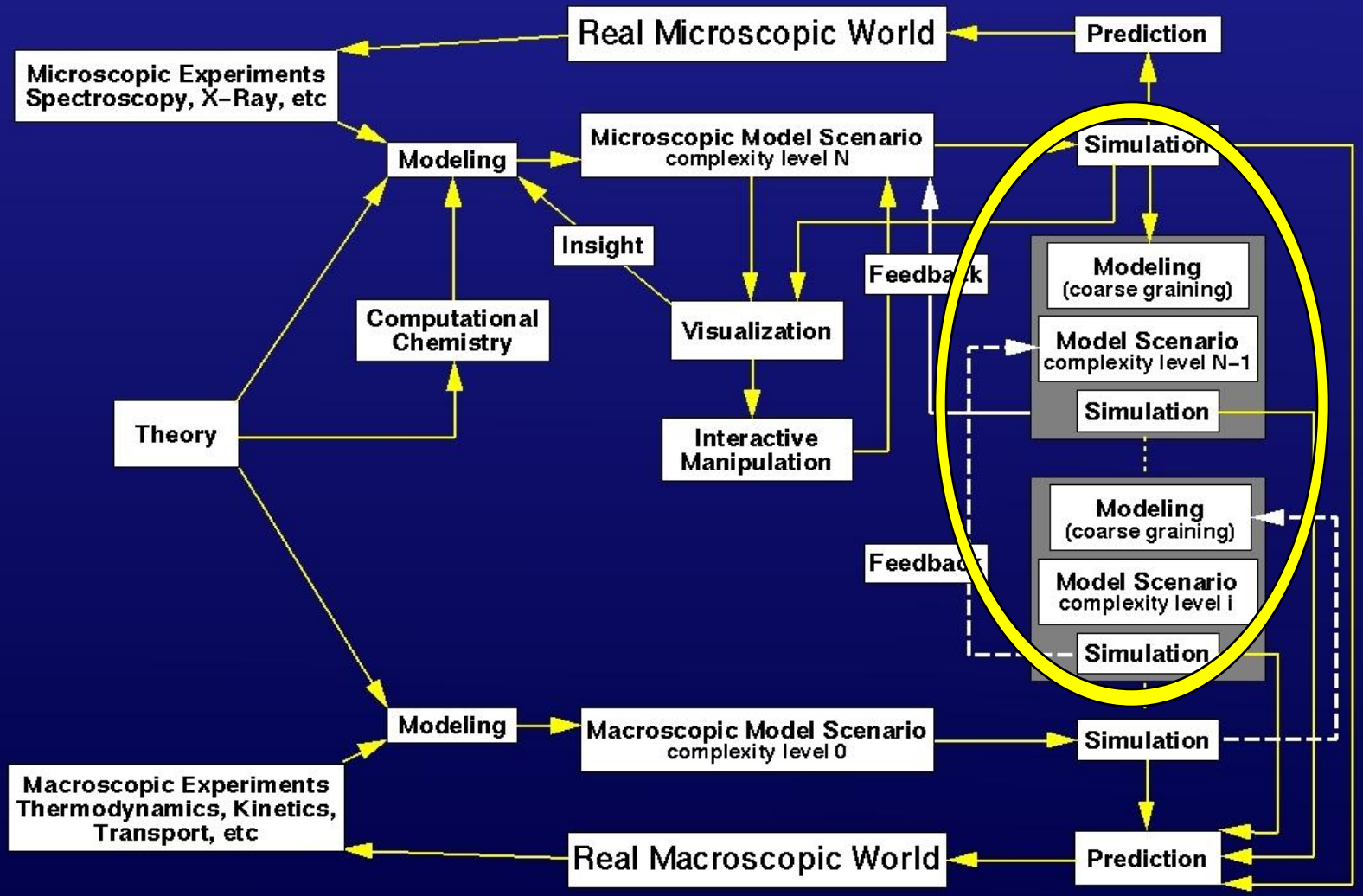
Tim Clark formulated the present situation of the modeling community recently as "Soothsayers or Scientists"

What will be the future?
The scale coupling problem



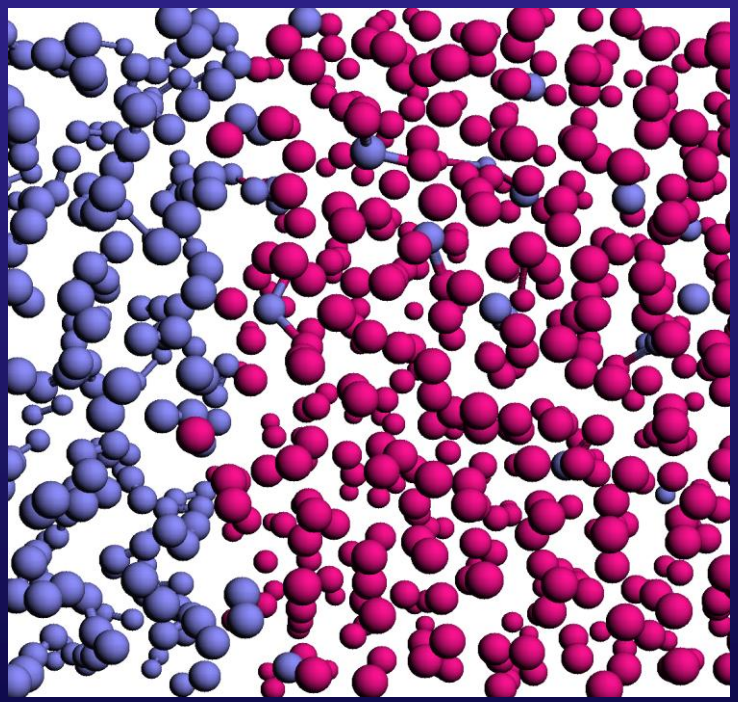
from Markus J. Buehler CMDF, CalTec

An Example from Materials Research: High Pressure Synthesis Pattern Formation

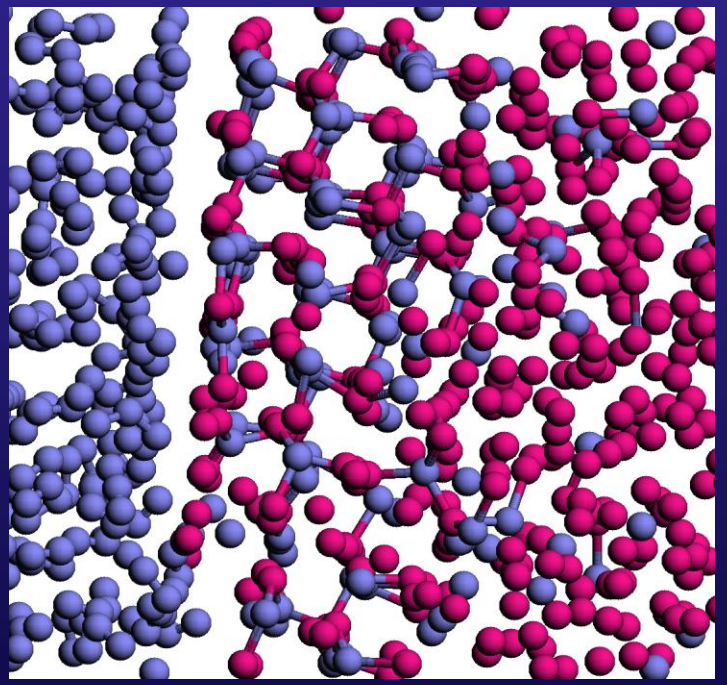


Hochdrucksynthese von GaN bei 2800 K

p = 50 kbar

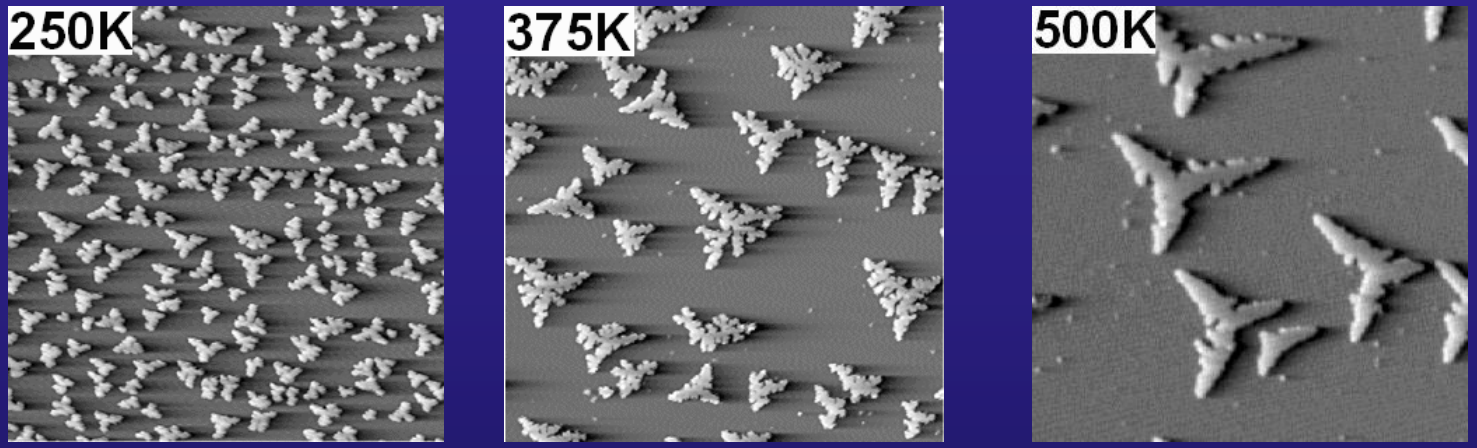


p=200 kbar

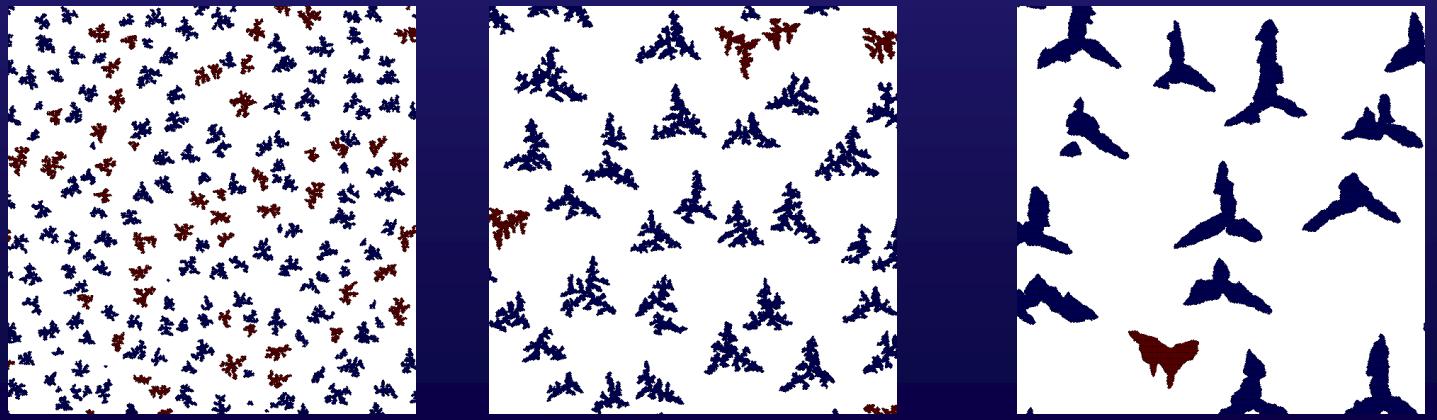


Molecular dynamics simulation K. Albe, TU Darmstadt

growing islands of Iridium on Iridium (111) surface



Experiment (C. Busse/Th. Michely, RWTH Aachen, Germany)



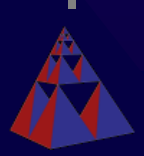
Kinetic Monte Carlo Simulation (K. Albe, Darmstadt, Germany)

Strategies for the Future

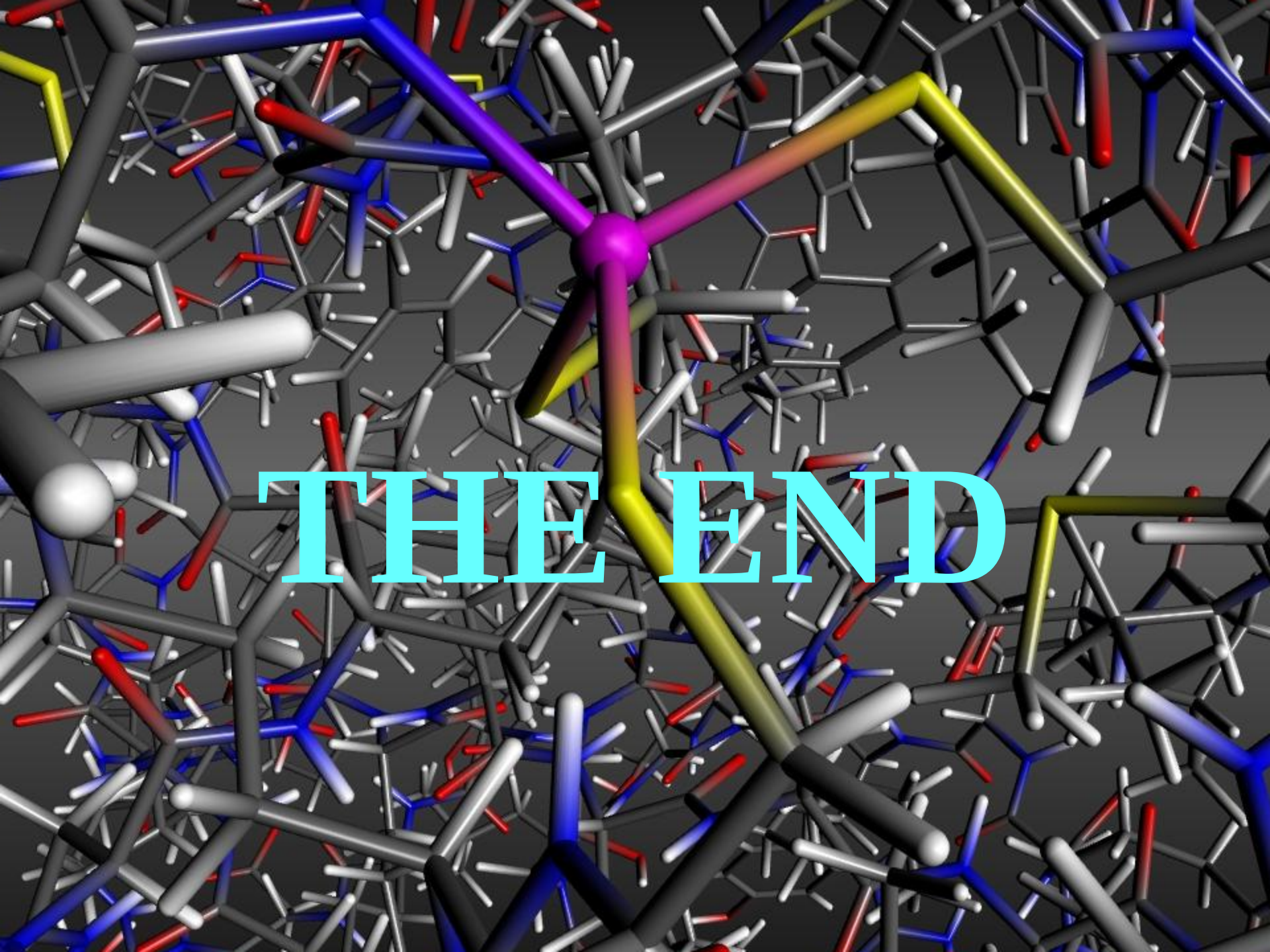
Solve the multi-scale problem

Introduce multi-scale multi-paradigm simulations

Invest in translational science




Thanks to all members of my group
who contributed to our development
over the last 25 years


THE END