Implementing a modeling software for animated protein-complex interactions using a physics simulation library

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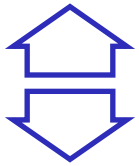
Existing Tools for Protein Animations

Time consuming operations using multiple tools

Molecular modeling software

- Atomic coordinates

.... (PyMol, Chimera)

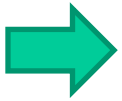


Gap

Generic 3D animation software

- Objects made of polygon meshes
- Photorealistic rendering
- Movements by bones

.. (Maya, Cinema4D, 3DMax, Blender)



Recent Techniques

- Motion tracking & data sharing
- Physics simulation
- Particle method

Making Protein Animations Biologically Correct

The protein movements in the cell

- integrate structural biology evidence
- additional probes by biophysical techniques (AFM)
- computer simulations

The Movies

- a direct description
- speculation and propositions due to insufficient experimental data
- costly operations with current software

--- *free software & resources are in demand*

UCSF Chimera

Molecular graphics & modeling software

- PDB models
- Interfaces to molecular simulation
- Basic animation
- Open source free soft (0.6M lines)
- Scripting with Python API
- Win/Mac/Linux (64bits)

Writing add-on tools

- difficulties of a big complexity
- programing works are nightmare

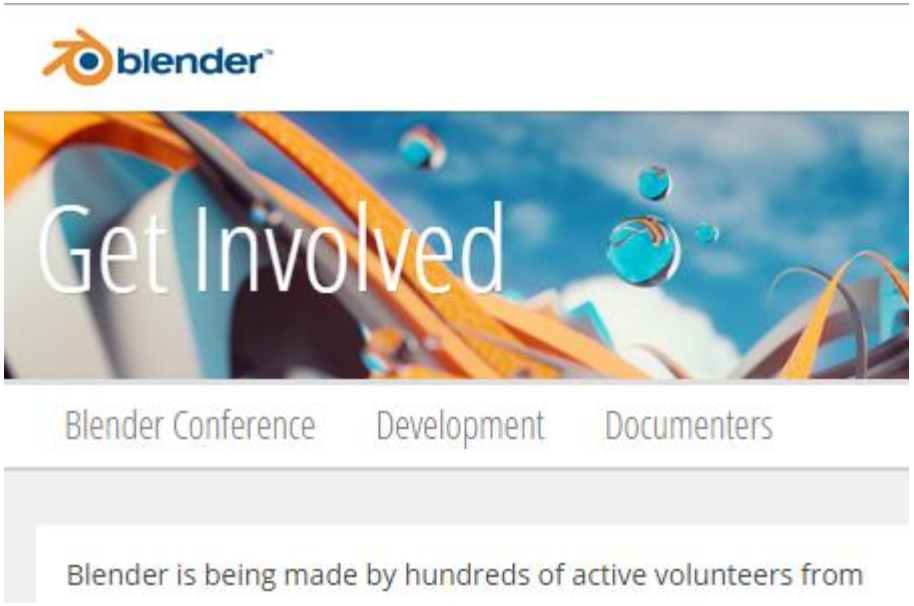
for Molecular Movie Scripting

- Nice & big challenge
- Could be separated

Blender

A 3D computer graphics modeling & animation software

- Full function for polygon models
- Game engine (Bullet)
- Photorealistic rendering
- Open source free soft (1.4M lines)
- Scripting with Python API
- Win/Mac/Linux (64bits)



Writing add-on tools

- difficulties of a big complexity
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for Molecular Movie Scripting

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Requirements

for a molecular animation software tool

- Collision detection and soft-body dynamics
  - no penetration
  - impact and friction between molecules
- Interactive modeling for macromolecules
  - hundreds of proteins
  - the reaction paths of the interacting molecules
- The scripting of molecular animation
  - molecular interactions saved in an accessible file
  - sharable among researchers

Our Original Software Development

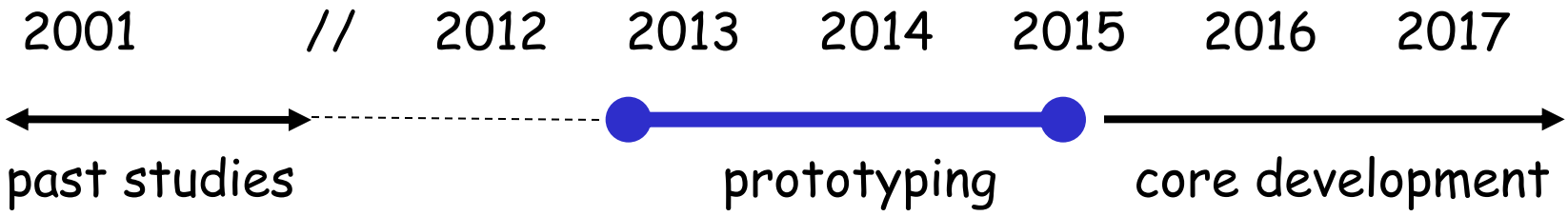
The script editor

- Objects of protein shapes made by atomic coordinates
- The script of movements and interactions
- Multi-scale modeling facility

Because

- Examine a modern software design
- Share models and animation scripts
- Add in-house software code into the system
- Test novel algorithms for visualization tasks

Schedule :



Luxinia : a software tool kit

3D open-source game engine

by Dr.Christoph Kubisch, at Otto von Guerick Univ.

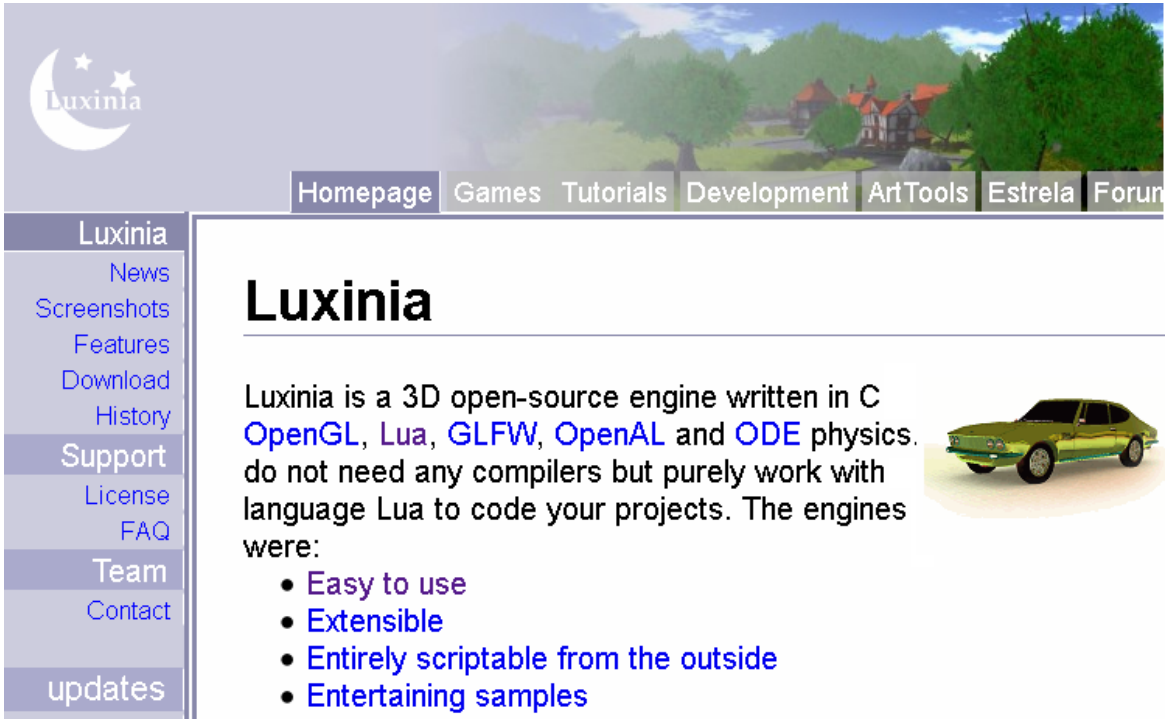
Features

- Fast and free
- Independent
- Extensible
- Scriptable

Specialties

- Particle Methods
- GPU shader

  + volume renderings

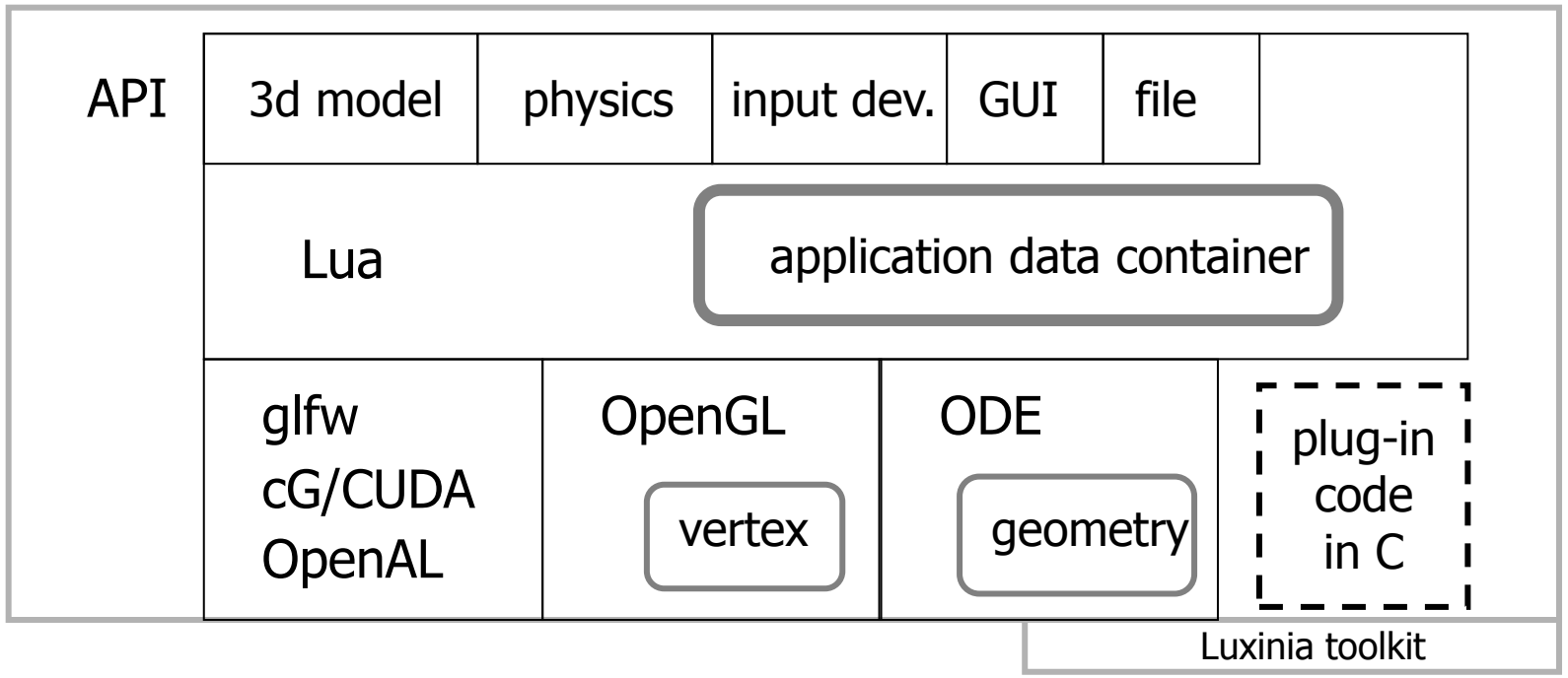


ver 1.400 on Win32 (2009)

A Lua based game engine

- The hierarchical data organized in Lua for the application data container
- Various engines available for smart phones:

  Corona, Marmalade, Cocos2dx ...



Adequate for the rapid prototyping

Programming Language Lua

Lua is a confirmed language

- Useful in describing complex hierarchical application data
- Easy to embed in an application programs
- The language is designed to be extensible
- External database supported
- Good runtime performance with JIT(just in-time compiler)
- Widely employed in commercial application programs & games

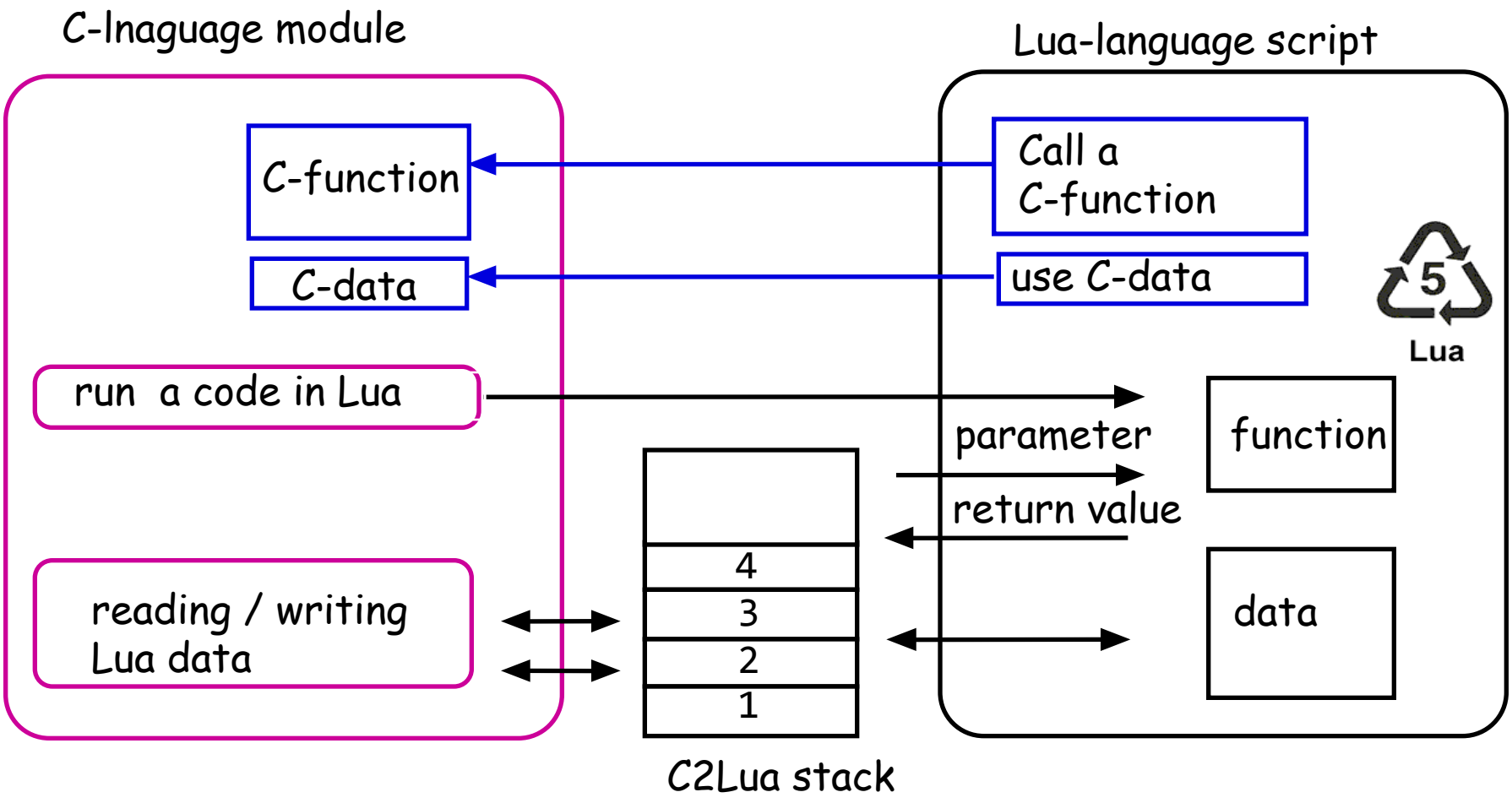
Free Software
www.lua.org

"Lua - an extensible extension language"

Roberto Ierusalimschy, Luiz Henrique de Figueiredo and Waldemar Celes Filho,

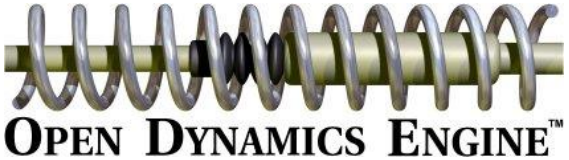
Practice & Experience 26(6), 635-652(1996)

Interface to a C-language module



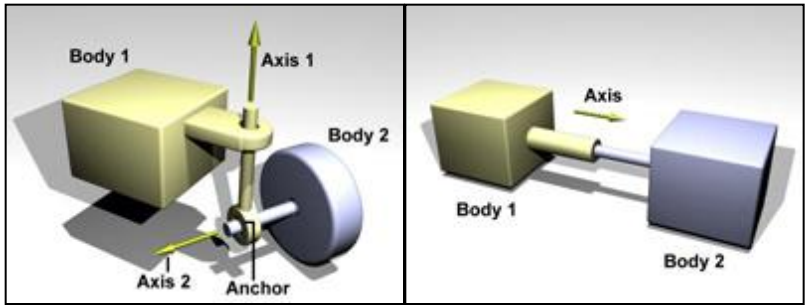
ODE: Open Dynamics Engine

- For simulating articulated rigid body structure
- C/C++ library Easy to embed in a application
- The first order integrator
- Multi-resolution hash tables or quad trees accelerates collision detection

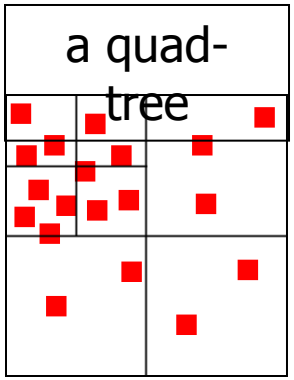


by Dr. Russell Smith

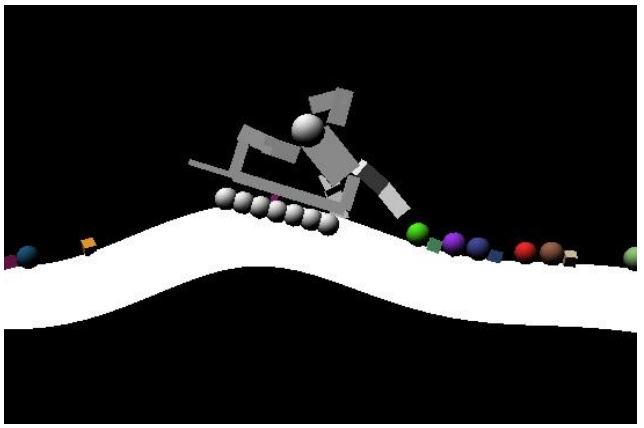
useful joint models



a quad-tree



a sample in Luxinia

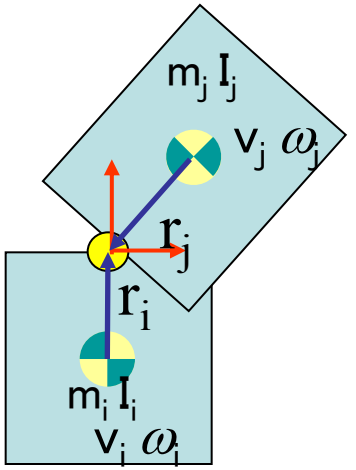


popular in robotics, action games and drive simulators (Google Drive)

Multi-rigid-body Contact Problems

Newton equation with constraints (penetration, joint)

$$\begin{aligned} M\dot{\boldsymbol{u}} &= \boldsymbol{f}_c + \boldsymbol{f}_e \\ \boldsymbol{u}[t+1] &= \boldsymbol{u}[t] + M^{-1}\Delta t \boldsymbol{f}_c + M^{-1}\Delta t \boldsymbol{f}_e \end{aligned}$$



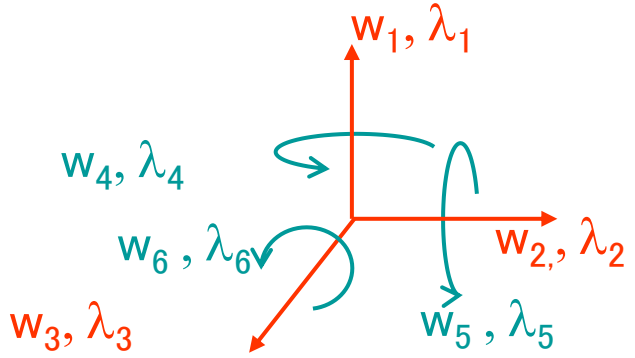
$\boldsymbol{w} = \boldsymbol{J}\boldsymbol{u}$ constraint coordinate

$$\boldsymbol{w}[t+1] = \boldsymbol{A}\boldsymbol{\lambda} + \boldsymbol{b} \qquad \begin{aligned} \boldsymbol{A} &= \boldsymbol{J}M^{-1}\boldsymbol{J}^t\Delta t \\ \boldsymbol{b} &= \boldsymbol{w}[t] + \boldsymbol{J}M^{-1}\Delta t \boldsymbol{f}_e \end{aligned}$$

λ: constraints

The Linear complementarity problem is solved (Lemke's algorithm)

$$\begin{bmatrix} 0 \\ 0 \\ 0 \\ w_4 \\ w_5 \\ w_6 \end{bmatrix} = \boldsymbol{A} \begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \boldsymbol{b}$$



from a slide by Dr.Shoichi Hasegawa

Coarse Grained Model

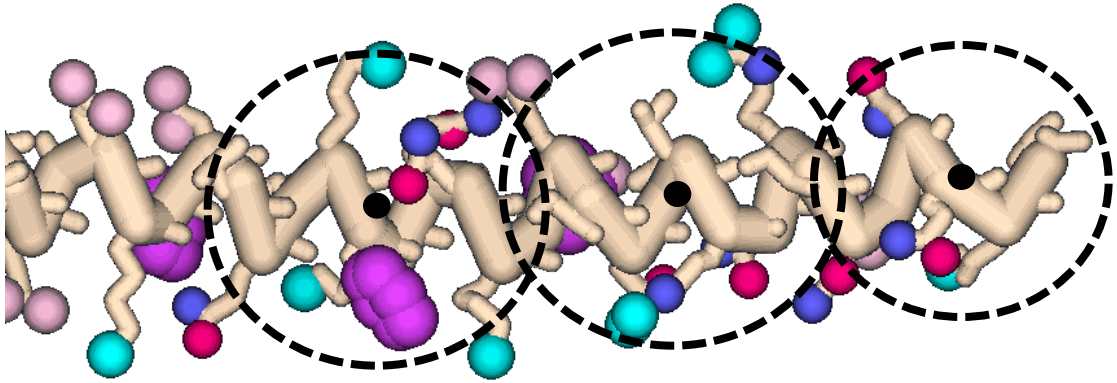
To simplify geometrical model of molecule

Example : myosin

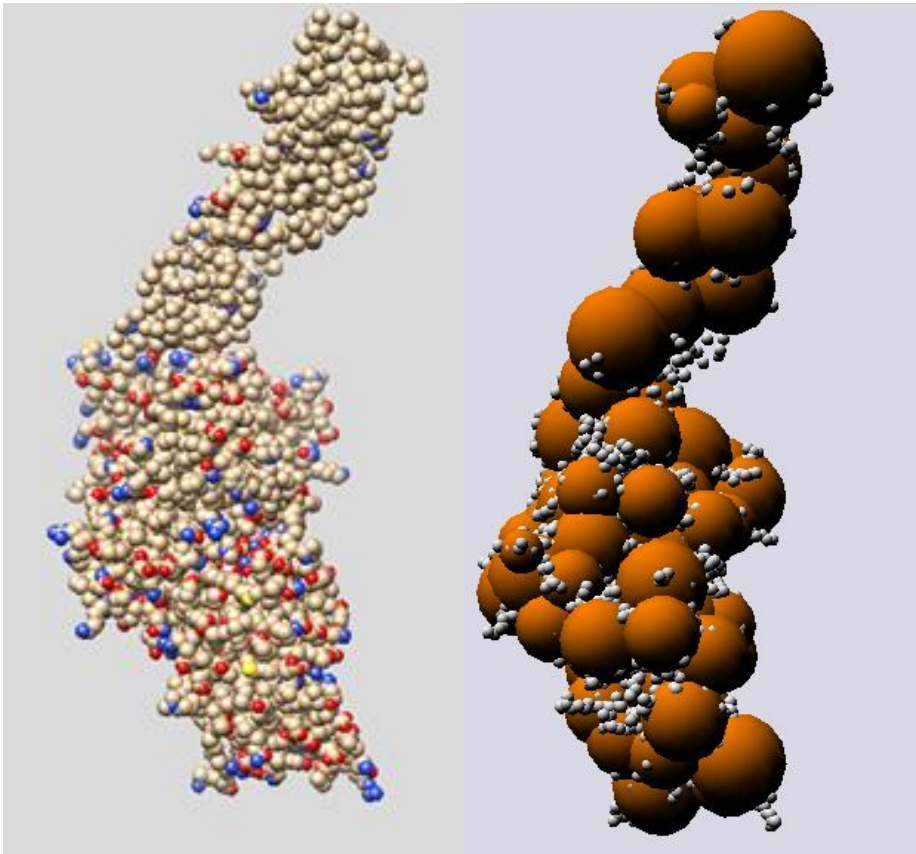
- 6788 atoms 1072 residues (2MYS)
- 86 sphere segments

  each segments includes

  average 79 atoms, 12 residues

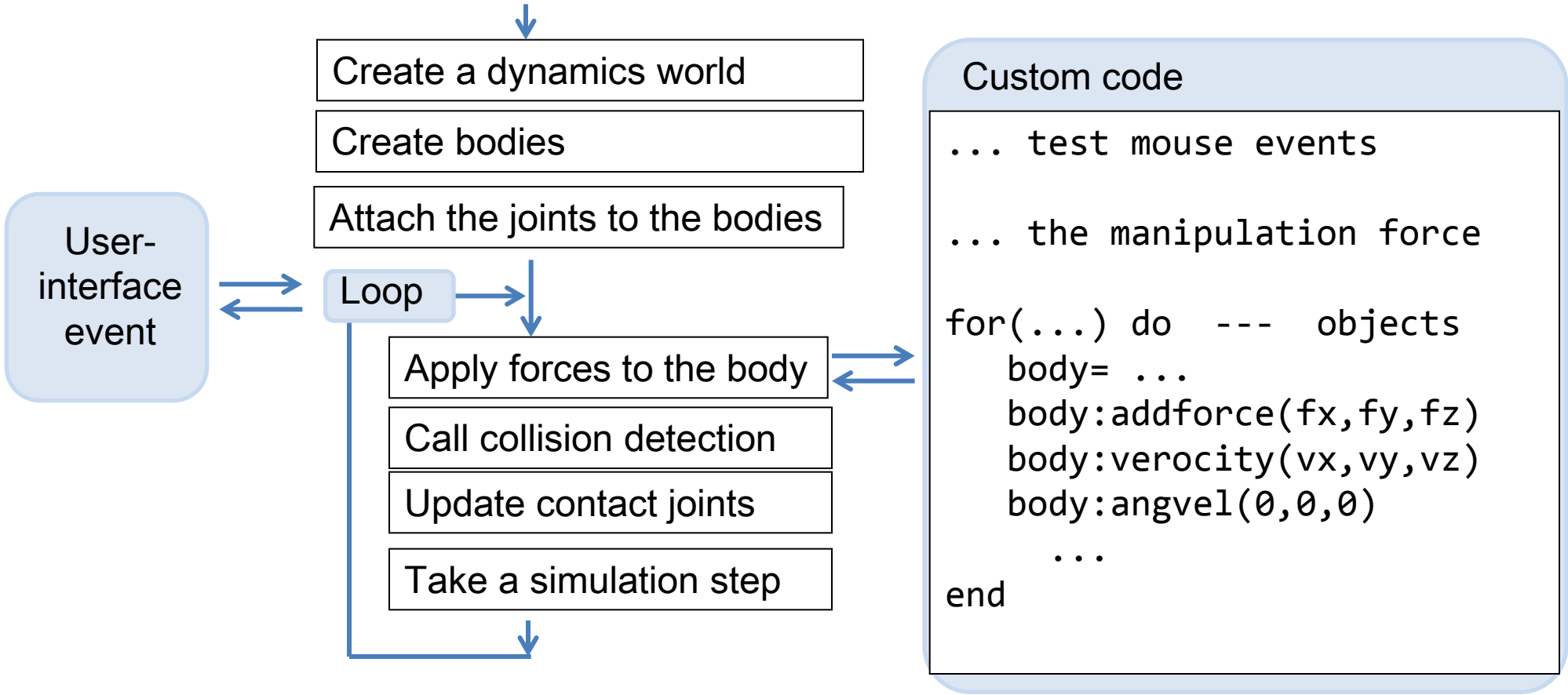


Each sphere segments are connected



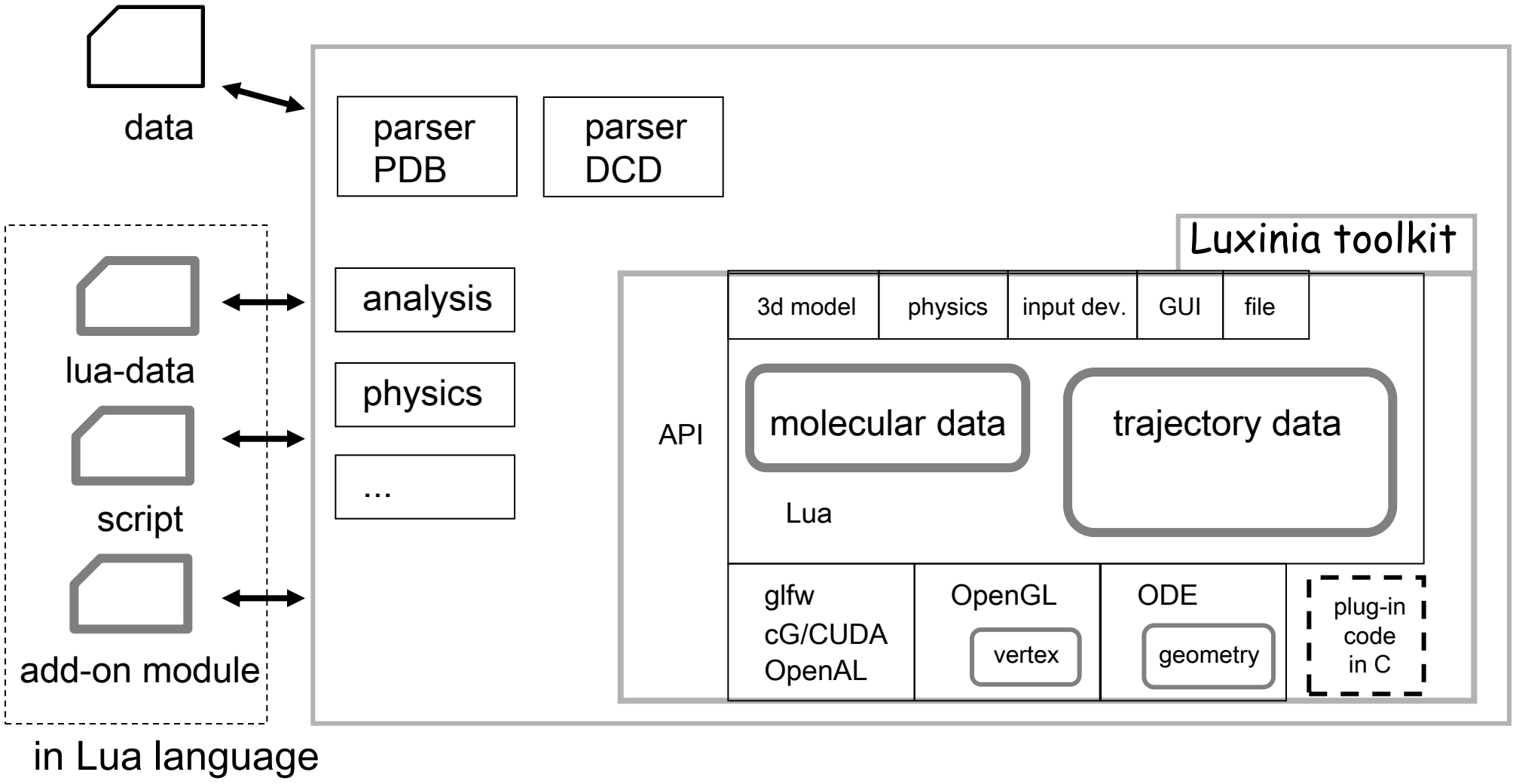
Coding with ODE

In the code of main loop manual interventions for the custom code allows various interactions of the model.



Lua is a Software Framework

- Lua functions are also in a script file



Planed Features

- ✓ Manipulation of protein object
  - Comprehensive user interface
- ✓ The time-line editor
  - key-frame based motion description
- ✓ Superimposing molecular dynamics
  - validations of precise molecular simulations
- Motion parts
  - Normal mode analysis
- Extensible script file
  - Offline editing and baking animations

... without photorealistic renderings, shadows and flashy effects

A Conceptual Comparison

* requirements

\+ additional general features

		general animation software (**Blende**r, Maya, etc.)	molecular graphics software (**chimera**, PyMol, etc.)	our game engine based tool
*	collision detection	optional	optional	N>1000
*	interactive modeling	good	good w/o collisions	good
*	movie script	limited w/o scientific context	limited	*under development*
+	molecular simulation	limited add-on scripts	good add-on scripts	*via add-on scripts*
+	modifying software system	complex difficult	complex very difficult	simplified moderate
+	photorealistic rendering	excellent with GPU	fair, portable (POV-ray)	*via add-on scripts* (raycast)

Game Engine for Molecular Model

- The rigid-body-model useful for molecular models
  - Coarse graining works to speed up
  - Real time manipulation of N>1000 objects
  - GPU accelerations are available
- Conventional molecular mechanics force field
  - Less speed up, even with GPU
  - Rich expertise of molecular simulation community
  - Scalable to the precise simulation results
- An ideal software design
  - The architecture of modern Game Engine would be useful

Conclusions

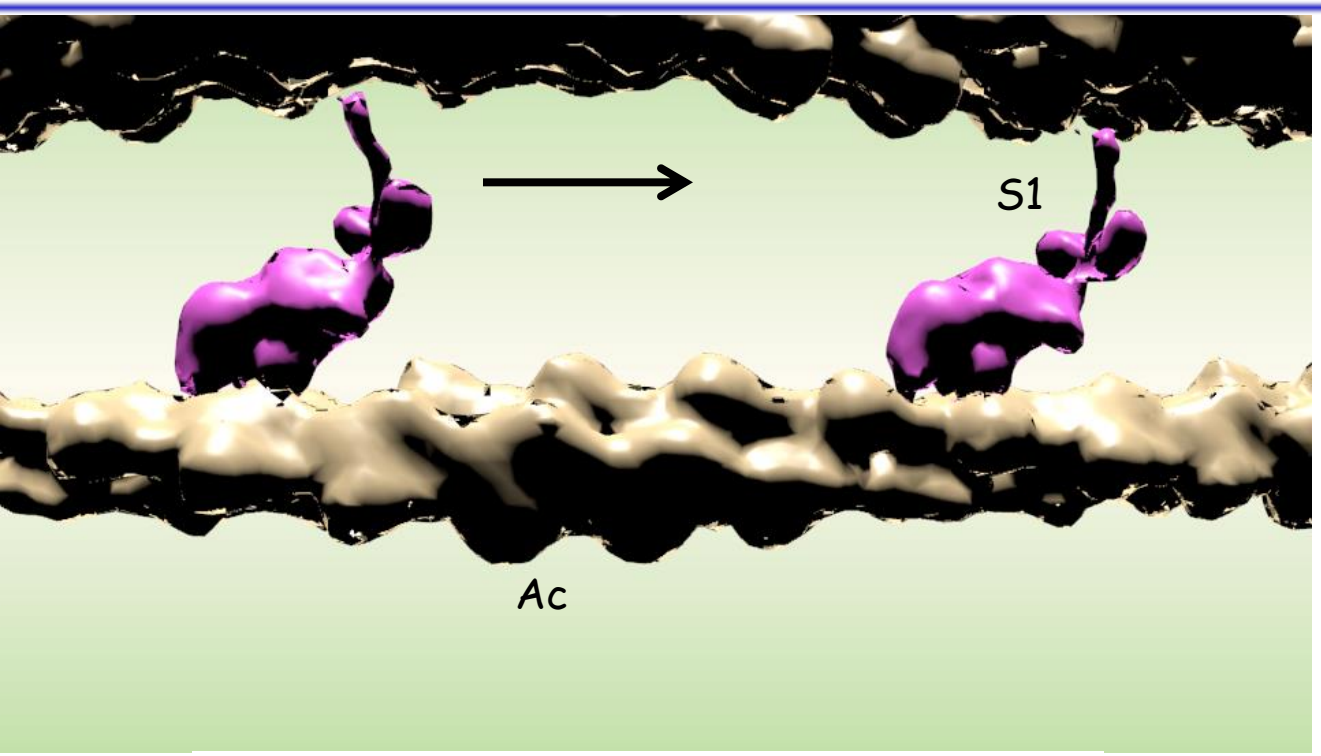
- Prototyping with a modern software development tool
  - collision detection and physics simulation of molecular models
  - Lua language as a software framework
- Prototyping
  - reaction path editor
  - script editor
- Further improvements
  - inclusion of legacy codes
  - script exchange

Acknowledgements

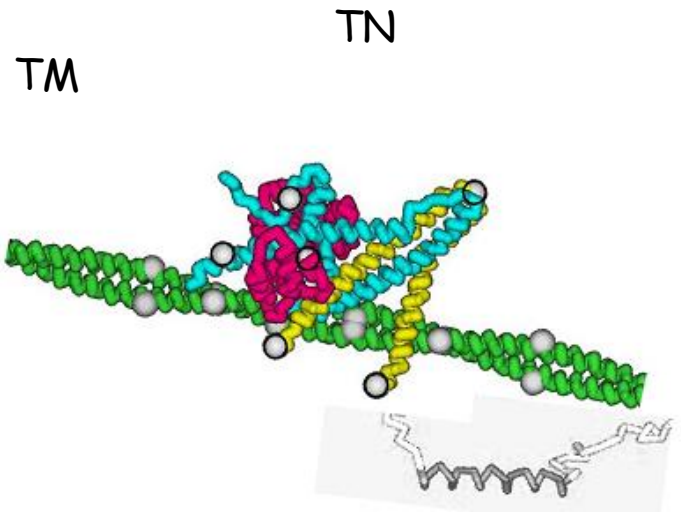
Prof.Shigehiko Kanaya (NAIST)

Supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Robotics" (No. 24104004) of The Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Target 2: Actin-Myosin



The force generation model



actin (Ac)
tropomyosin (TM)
troponin (TN)
myosin (S1)

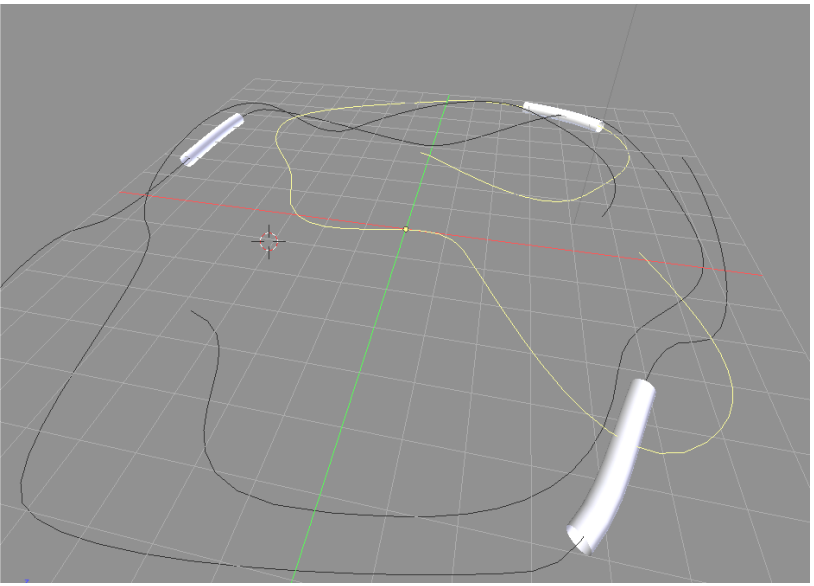
Movements based on observed FRET distances between TM and TN
Kimura et al(2008) J.Mol.Biol. 276

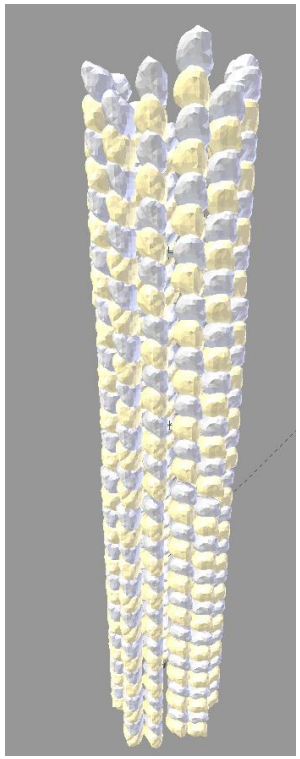
...with Prof.Miki (Fukui University)

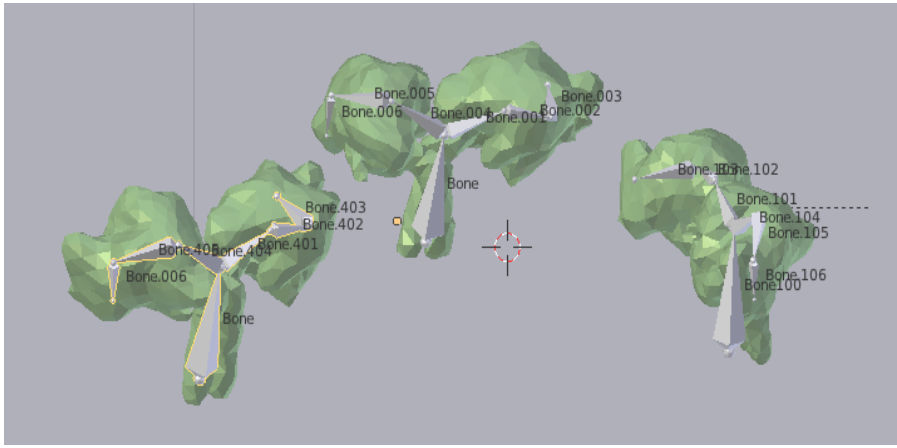
Target 1: Tublin-Kinesin

Our first work on blender

Visual examination of the in-vitro motility assay

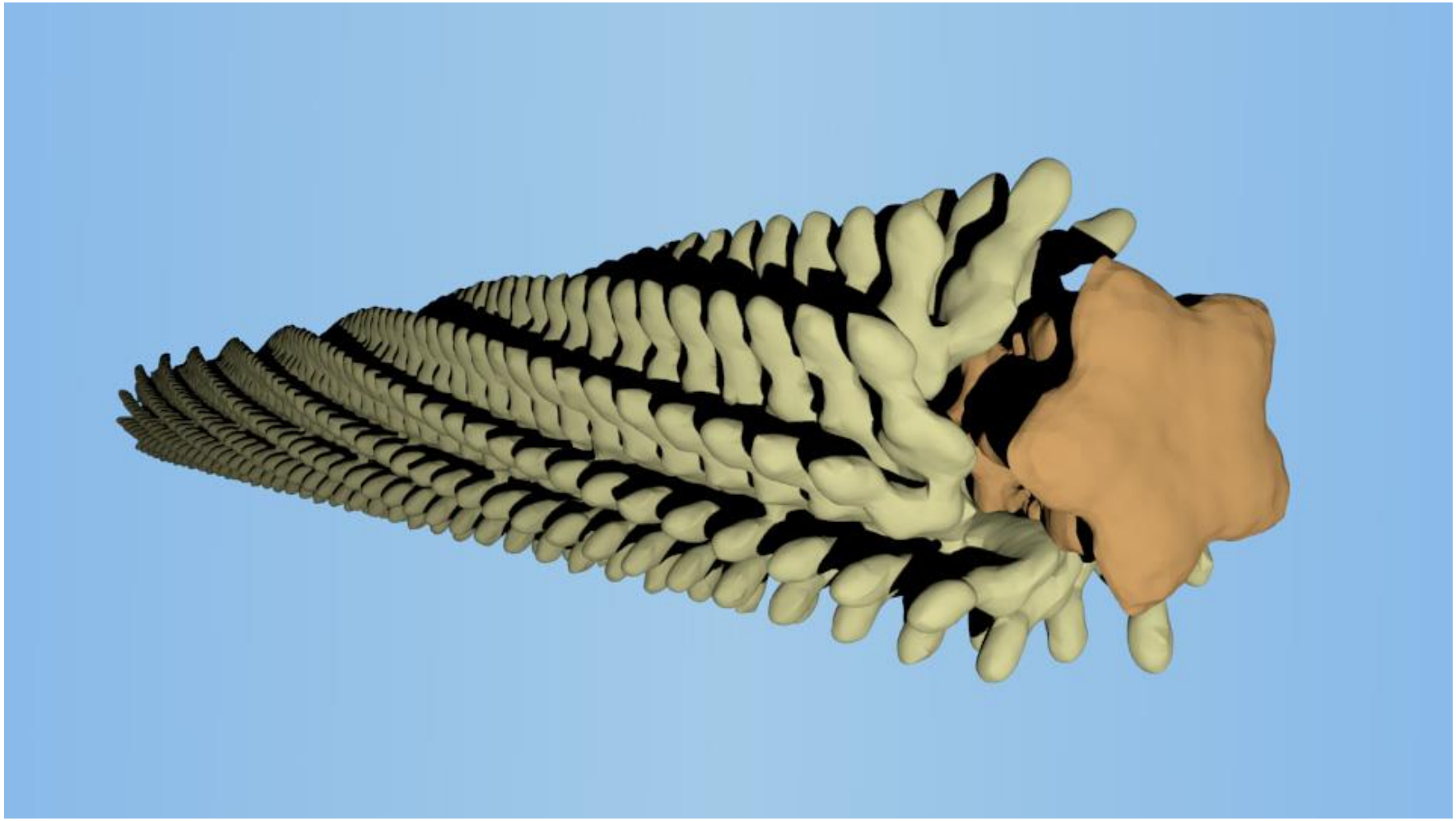






Target 3: Flagellar Filament

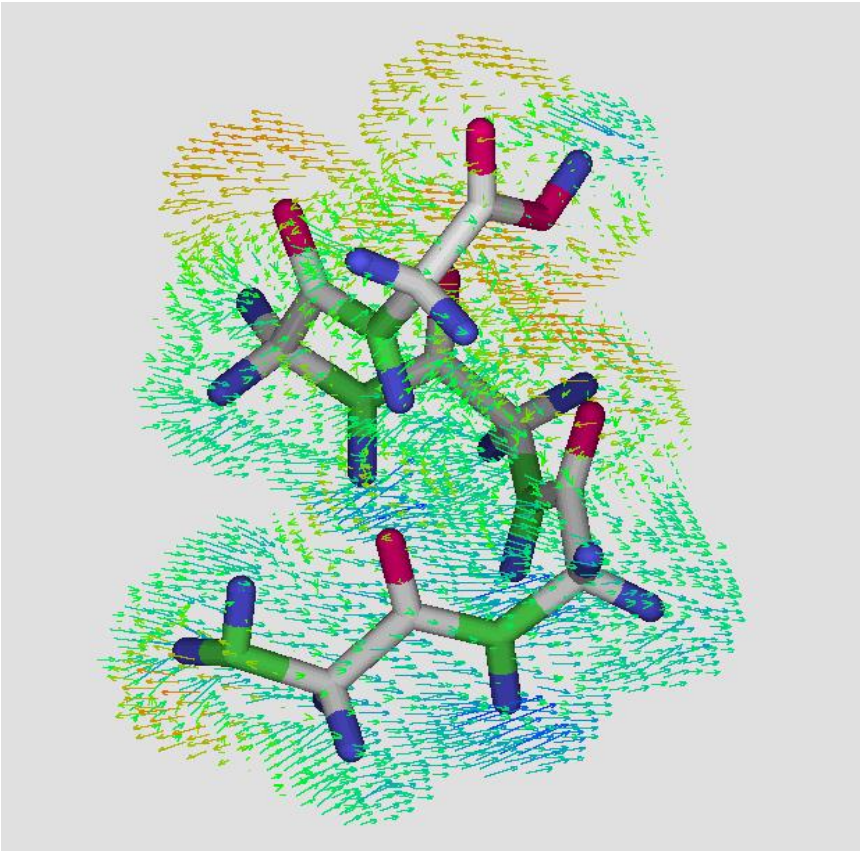
planed in 2015　flagellar filament motions: a free "cover" version



data by Dr.Namba, Osaka Univ.

Molecular Structure Browser : MOSBY

- A simple viewer program written in C
- Fast sphere renderer
- A plug-in extension mechanism is porposed (1998)
- Restructured by Lua (2005)



An example extension:
Gradient of the electrostatic potential
on the VDW surface of the molecule
by arrows, with colored by magnitudes

4-dimmensional sparse matrix by Lua

A result by fragment molecular orbital method with 5-mer poly-alanin helix conformation (Nakano, Komeiji, 2001)

Lua, a software architecture

Not only for game development, Lua also provides a software architecture for application software systems wider in scientific area