MCell4 with Python API - Status Update

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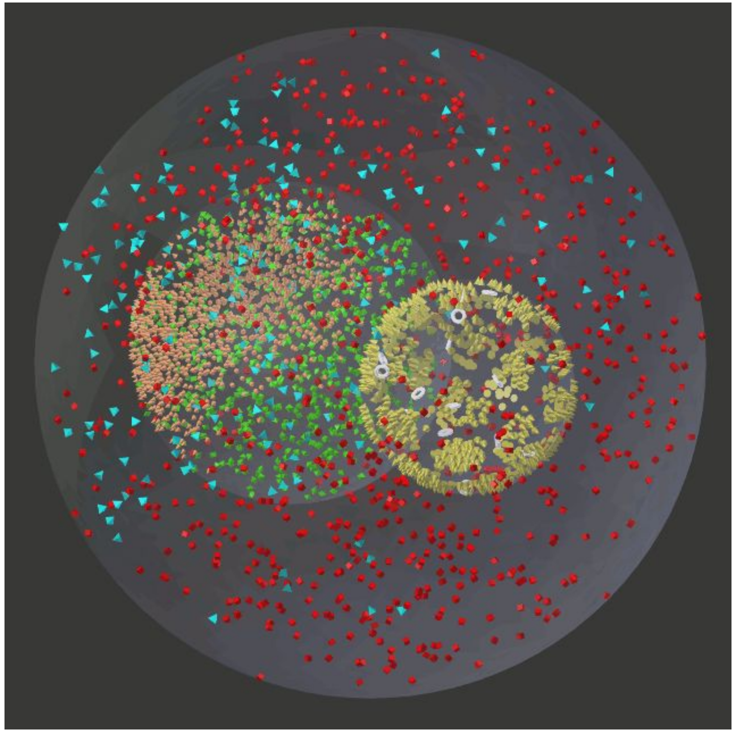
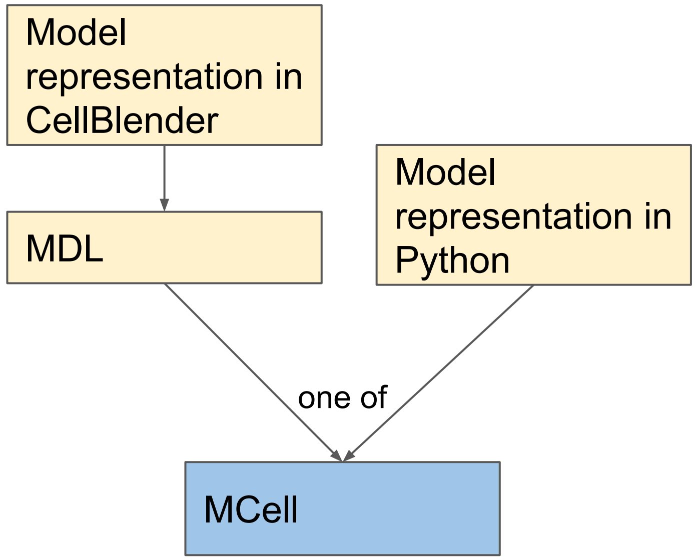


Current MCell and new Python Interface

- MCell3 uses as input a domain specific language called MDL (Model Description Language)
  - The definition is mostly static and prescribed, still capable to describe a wide range of processes
- Python provides capabilities to do any manipulations once the simulation is running such as:
  - Change simulated state based on what's going on in the simulation
  - Interact with external simulators


Model representation in CellBlender
MDL
Model representation in Python
one of
MCell

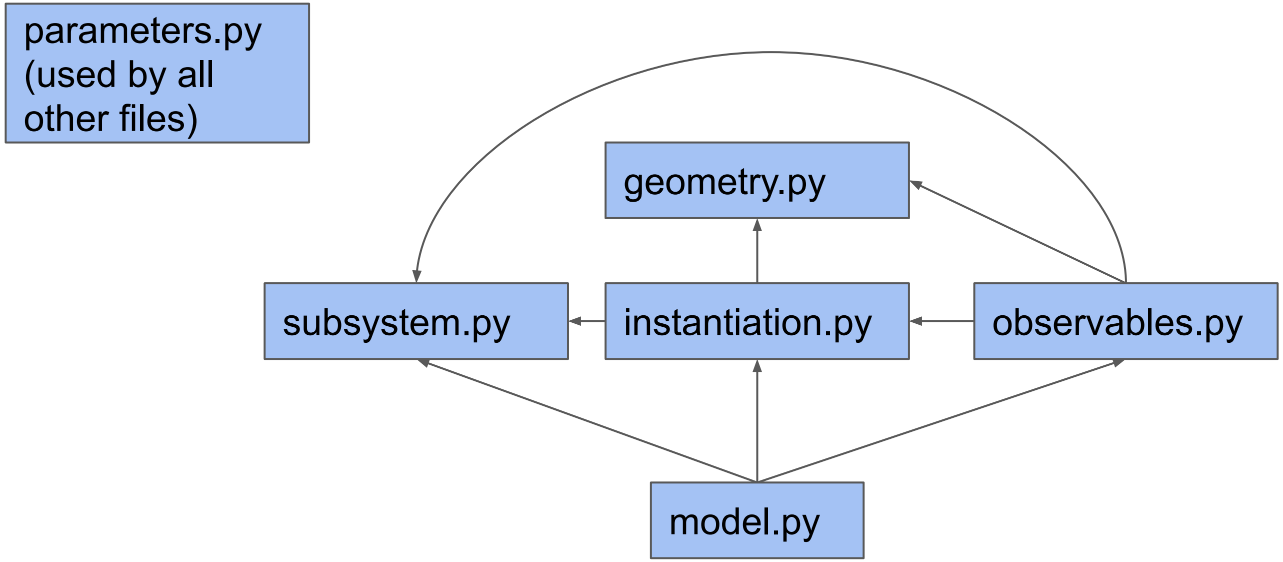
MCell4 - New MCell Implementation

- MCell3 is implemented in the C language
  - It has gotten complex over the >15 years of development
  - Practically impossible to parallelize, hard to do substantial changes

- New implementation in C++
  - Provides Python API
  - Prepared for parallelization
  - Easier extensibility
  - Native support for BioNetGen species and reactions

Base MCell4 Model Structure

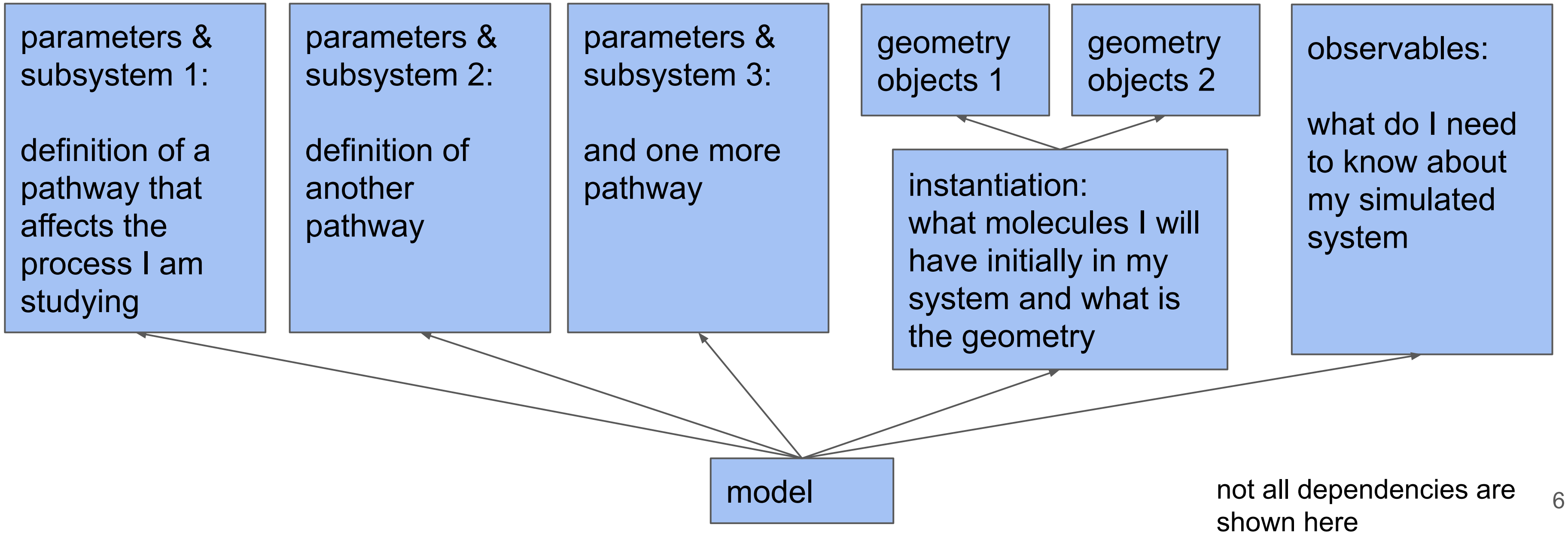
- Having a defined structure helps with orientation in models
- Allows to create reusable models and libraries



arrows show dependencies

Modularity

- Each subsystem (pathway) definition is independent and can be merged with others
- Requires uniform naming of substrates


parameters & subsystem 1:

definition of a pathway that affects the process I am studying
parameters & subsystem 2:

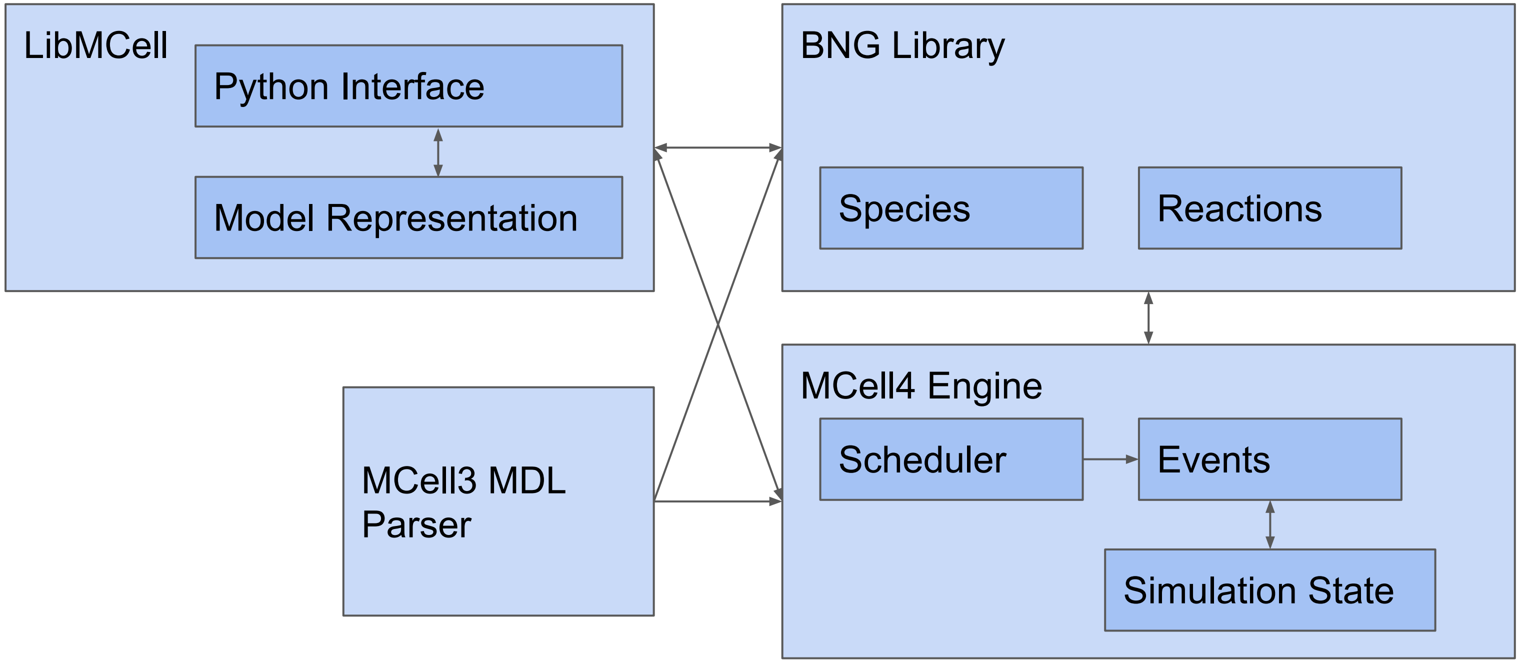
definition of another pathway
parameters & subsystem 3:

and one more pathway
geometry objects 1
geometry objects 2
observables:

what do I need to know about my simulated system
instantiation:
what molecules I will have initially in my system and what is the geometry
model

not all dependencies are shown here

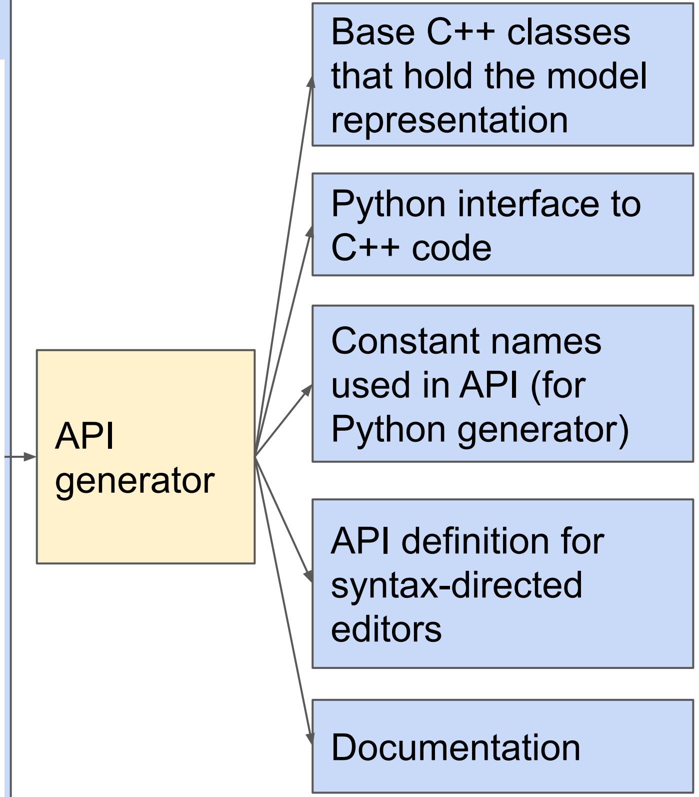
Overall Architecture of MCell4



Python API Definition and Generator

Definition of classes in YAML format

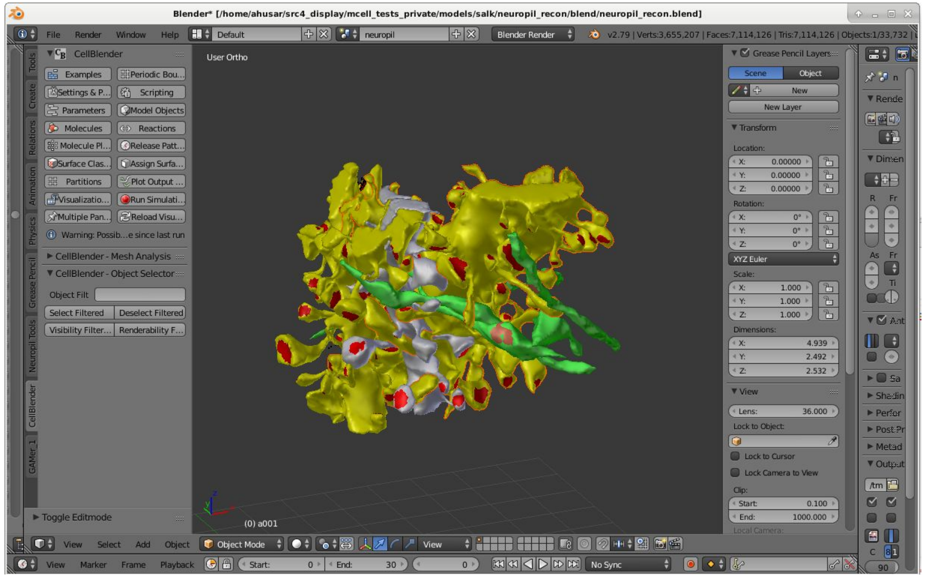
```yaml
Complex:
  superclass: BaseDataClass
  doc: |
     This class represents a complex molecule composed of molecule instances.
     It is either defined using a BNGL string or using a list of elementary molecule instances.
     On top of that, orientation may be defined.
     This class is used as argument in cases where either a fully qualified instance or a pattern
     can be provided such as in observable Count.

  items:
  - name: name
    type: str
    default: empty
    doc: |
       When set, this complex instance is initialized from a BNGL string passed as this argument,
       the string is parsed during model initialization so the molecule types it uses
       don't have to be defined before initialization.

  - name: elementary_molecule_instances
    type: List[ElementaryMoleculeInstance*]
    default: empty
    doc: Individual molecule instances contained in the complex.

  - name: orientation
    type: Orientation
    default: Orientation.DEFAULT
    doc: |
       Specifies orientation of a molecule.
       When Orientation.DEFAULT if kept then during model initialization is
       'orientation' set to Orientation.NONE for volume complexes and to
       Orientation.UP for surface complexes.
       Ignored by derived class Species.

  - name: compartment_name
    type: str
    default: unset
```

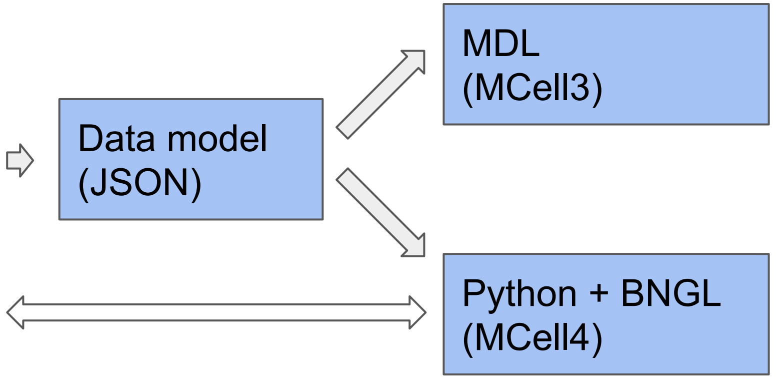

API generator
Base C++ classes that hold the model representation
Python interface to C++ code
Constant names used in API (for Python generator)
API definition for syntax-directed editors
Documentation

BioNetGen Library

- The preferred way to define species and reactions in MCell4 models is in the BioNetGen language
- Implemented new BNG library
  - Existing NFSim is very useful but hard to maintain
  - Designed with independence on MCell4 in mind, hopefully useful in other tools
  - New implementation contains:
    - BNGL parser, classes to represent BNGL constructs, BNG reactions engine
- BNGL parser testsuite with 59 tests
- Created a proposal on improved surface reaction definition in BNGL
- Current status
  - Validated with complex models of SynGAP and CaMKII holoenzyme & other BNGL tests
  - Each complex may have just one compartment for now
  - No support for BNGL functions

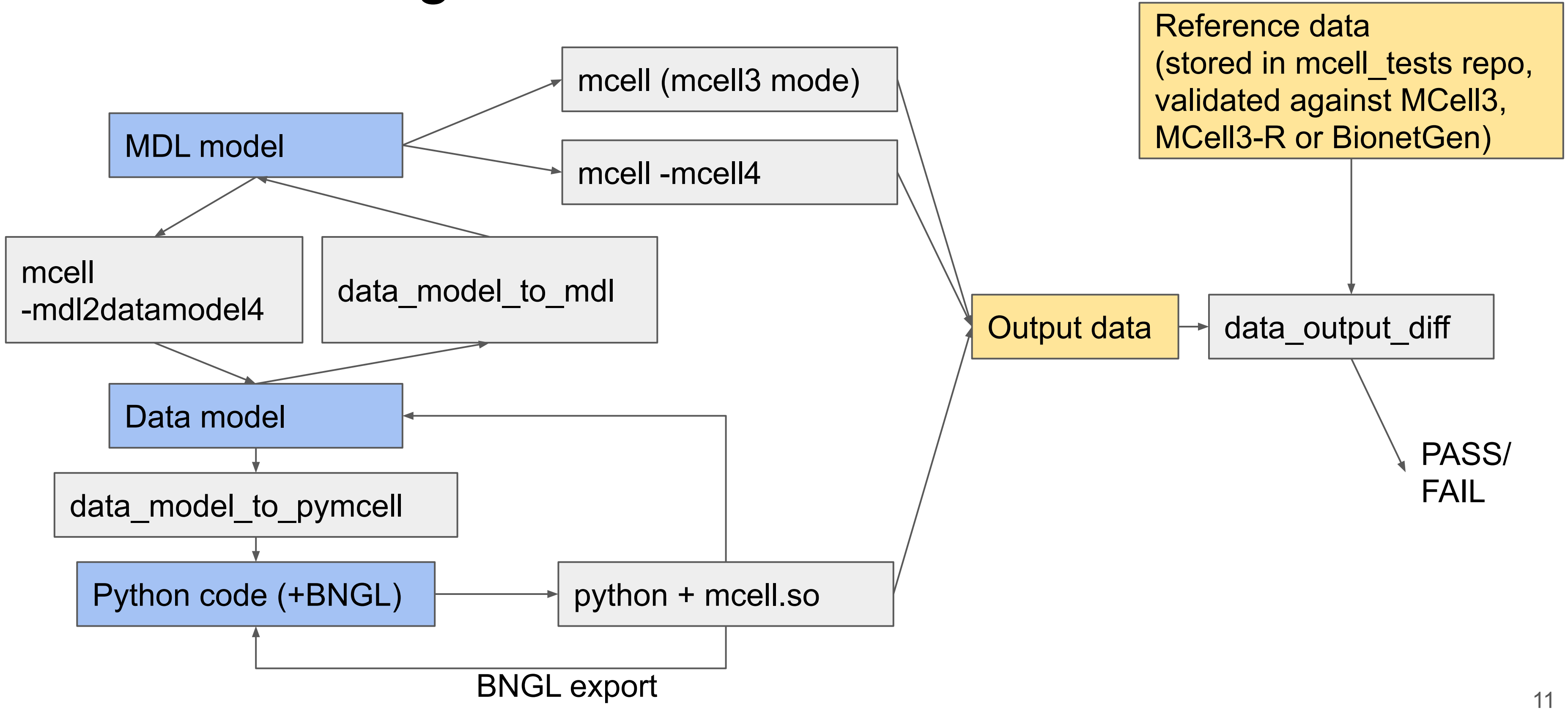
MCell Usage Scenarios and Model File Formats





- Code history, comments, code reviews

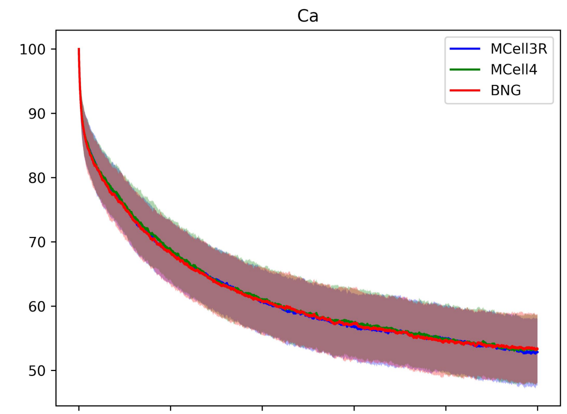
MCell4 Testing

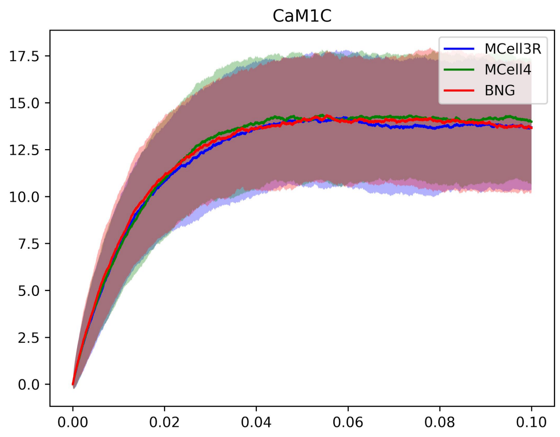


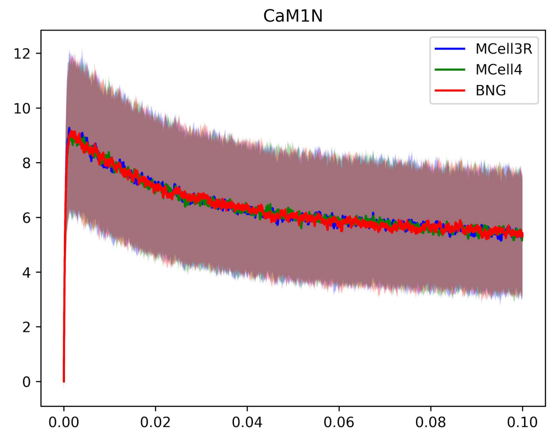
Testing & Build Infrastructure

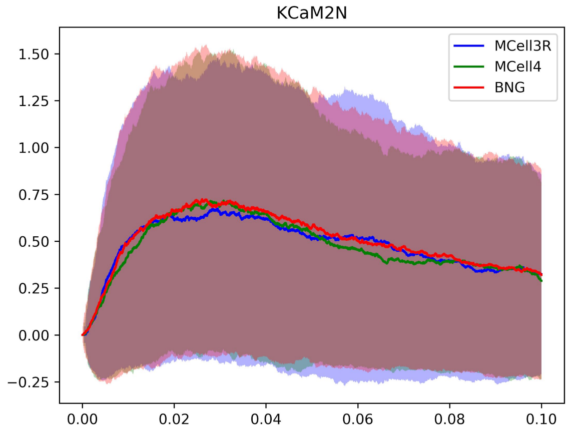
- New Python implementation of a test & build infrastructure
- New tests:
    - MDL: 214
    - Python/MCell4: 38
    - BNGL: 107
    - Data model: 27
- Total number of tested variants with conversions to various variants (MDL, Python/MCell4, BNGL, data model):
    - MCell4: 1184
    - MCell3: 433
- Single script to build CellBlender package and test it
- Public CellBlender releases 3.4.0, 3.5.0, and 3.5.1
- Virtual machines for build on MacOS, Linux Centos 6-7, Linux Debian 8-10, Windows 10

Example of Validation - CaMKII Holoenzyme Model







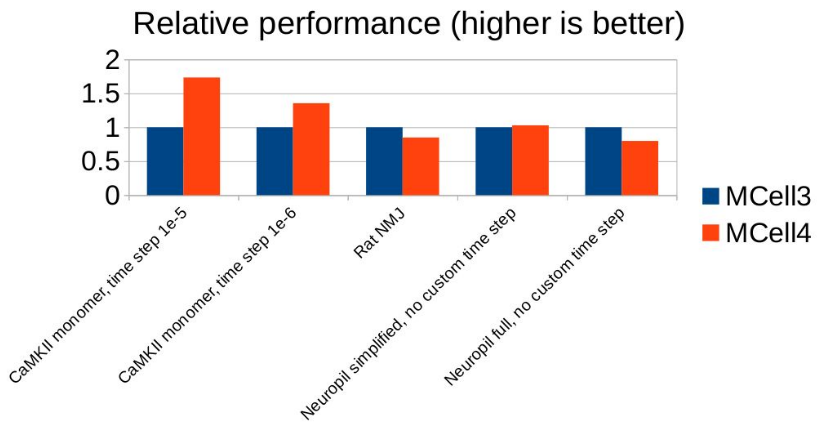


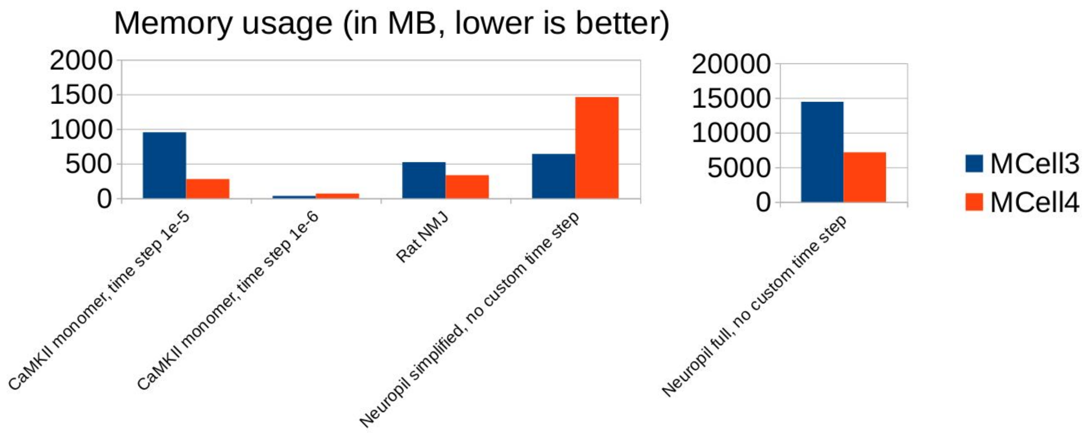
- 100 000 iterations (0.1 s), average from 512 runs with different random seeds, BNG values are obtained with NFSim, bands represent standard deviation
- Molecules in MCell3R and MCell4 use diffusion constant 1e-3 cm^2/s to emulate well-mixed solution (usual value is around 1e-6 cm^2/s)
- CaM1C - CaM(C~1,N~0,camkii), CaM1N - CaM(C~0,N~1,camkii), KCaM2N - CaMKII(Y286~P,cam!1).CaM(C~0,N~2,camkii!1)

Demonstration

- Model export from CellBlender
- MCell4 Python model example
- Debugging in Eclipse

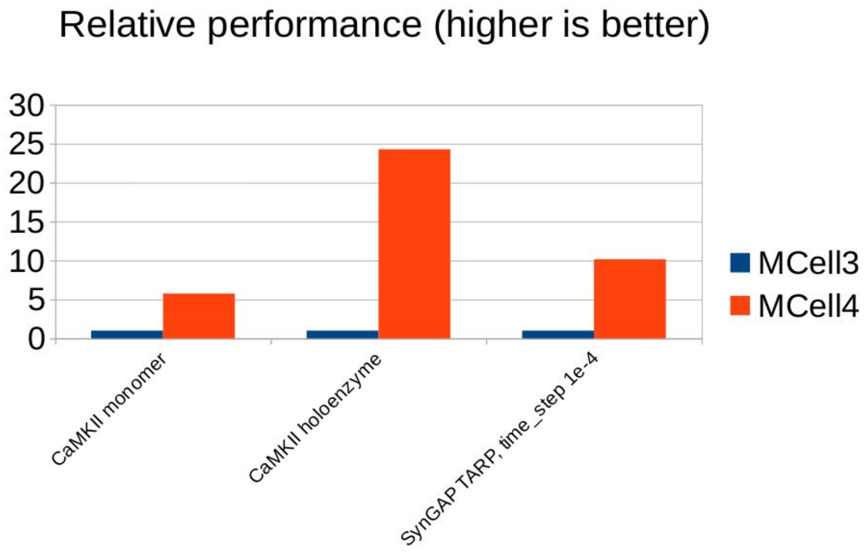
Performance Results - MCell3 Reactions

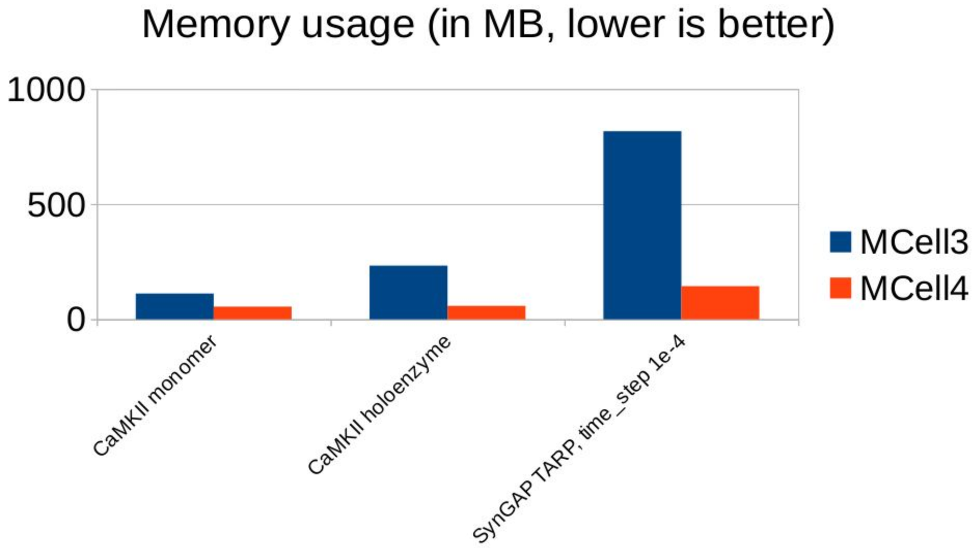




- Single-threaded execution, Linux Debian 9, AMD Ryzen 9 3900X @3.8GHz
- MCell3 3.5.1, MCell4 4.0.internal.8

Performance Results - BioNetGen Reactions





Conclusion

- Python interface
  - Subsystems (sets of species and reactions) as independent modules
  - Provides a way to model features that are not directly supported
  - Integration with external simulators
  - Usage of Python debuggers & syntax-directed editors
- New MCell4 implementation
  - Extensible, prepared for parallelization
- New BioNetGen library
  - Used for all species and reactions in MCell4
  - Planning to release it as a standalone library
- Automatic build and testing system

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Backup slides

Features and Code Statistics

- Main features missing in MCell4 compared to MCell3:
  - Custom time step (needs to be validated)
  - Periodic boundary conditions
  - Checkpointing
  - Trimolecular reactions (not planned)
- Improved dynamic geometry
  - Changing geometry based on user's Python code

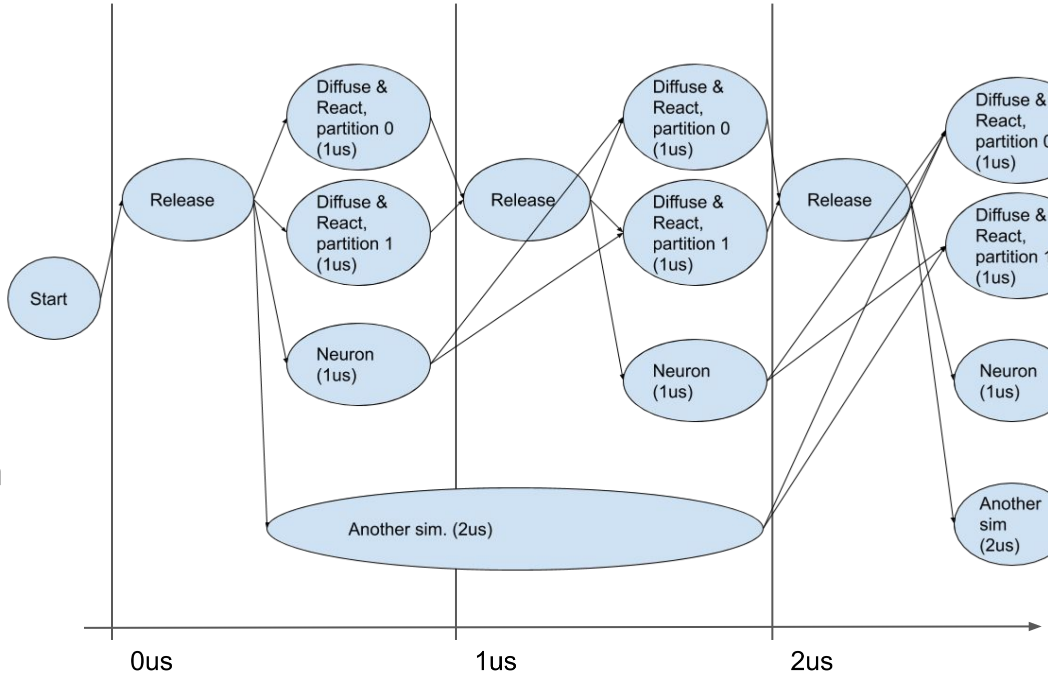
- Lines of C & C++ code (without comments)

MCell3	NFSim + nfsimCInterface
50 516	26 851

MCell4 + libMCell	libBNG
22 236	8 324

Integration with Other Simulators

- Need to model
  - external environment
  - physics not covered by MCell
- Data exchange
- Python to define the interactions
- Allow parallel execution of included simulators
  - e.g. using task-based parallelism


Start
Release
Diffuse & React, partition 0 (1us)
Diffuse & React, partition 1 (1us)
Neuron (1us)
Another sim. (2us)
Release
Diffuse & React, partition 0 (1us)
Diffuse & React, partition 1 (1us)
Neuron (1us)
Release
Diffuse & React, partition 0 (1us)
Diffuse & React, partition 1 (1us)
Neuron (1us)
Another sim (2us)
0us
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