CARDIAC ELECTROPHYSIOLOGY WEB LAB

A technical tour

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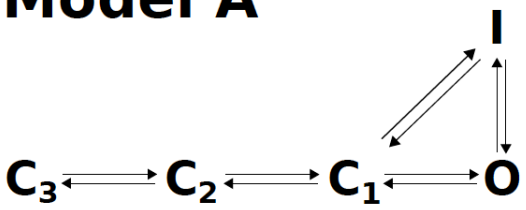
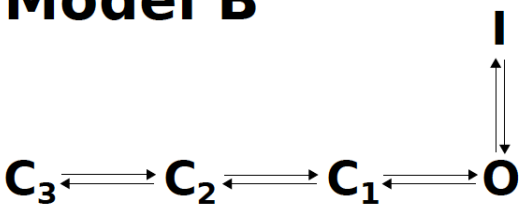
Different literature structures for I_{Kr} (cardiac ion current)

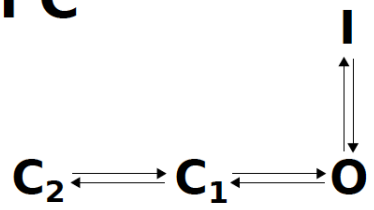
Model A



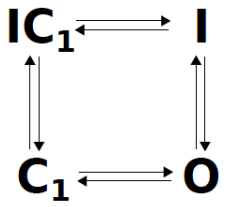
Model B



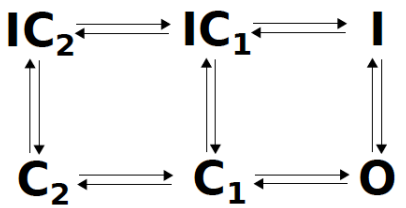
Model C



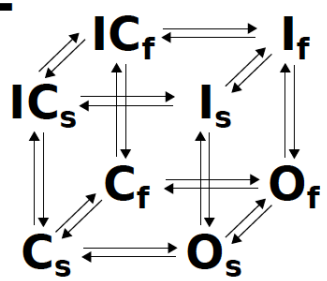
Model D



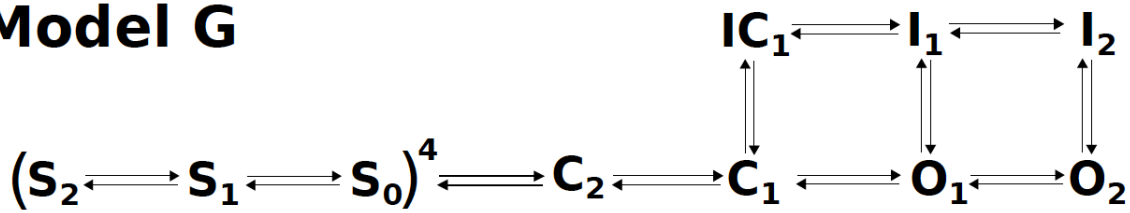
Model E



Model F

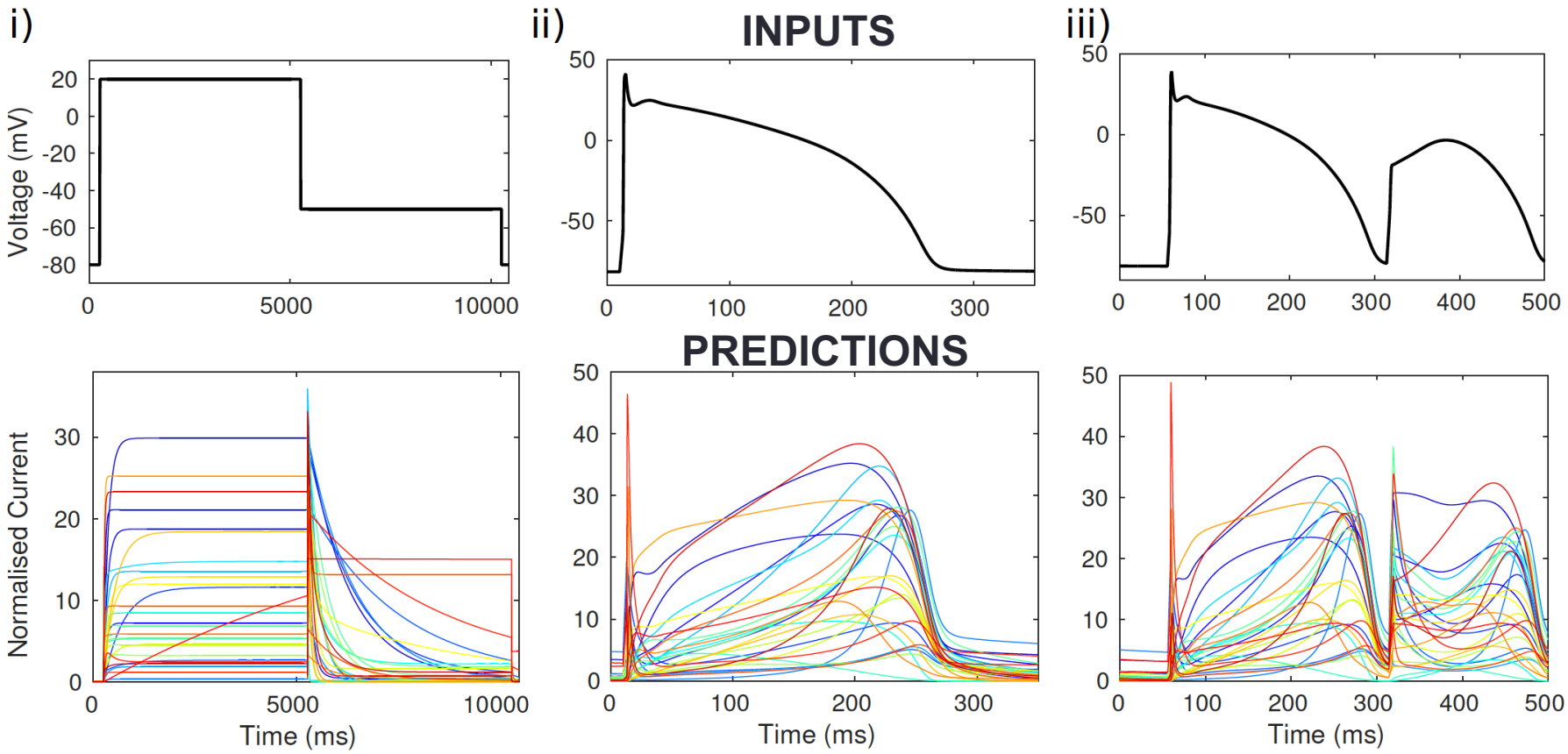


Model G



C = closed
O = open
I = inactivated

Different models, different predictions



(some of this variation is to be expected… but which model should the FDA use?)

A vision of the future…

- Knowledge about mechanisms is captured in quantitative models
- Best experiments to do are therefore the ones that best [select and] parameterise the model
- Provide these to experimentalists
- Automate model development
- Deploy in the Virtual Physiological Human!

Motivation

EMBL-EBI

BioModels Database

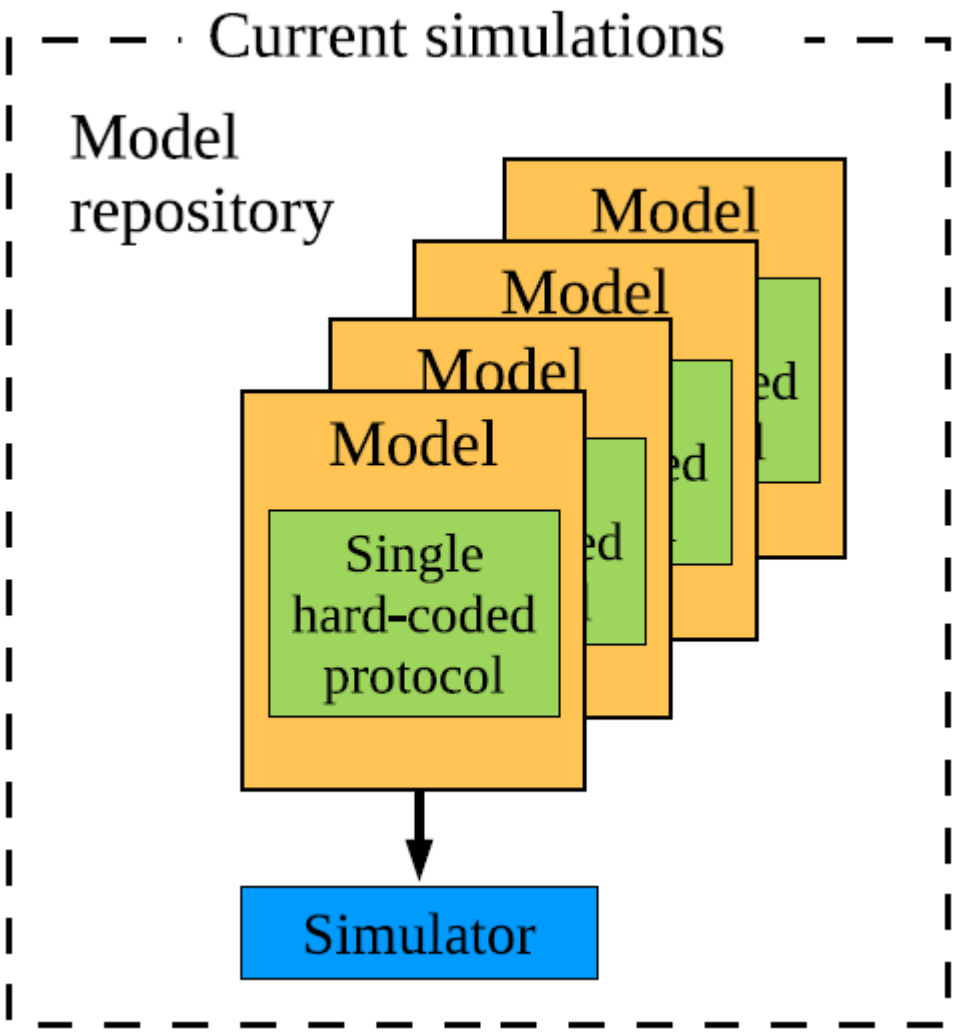
Models Home | Exposures | Documentation

You are here: Home / Physiome Repository

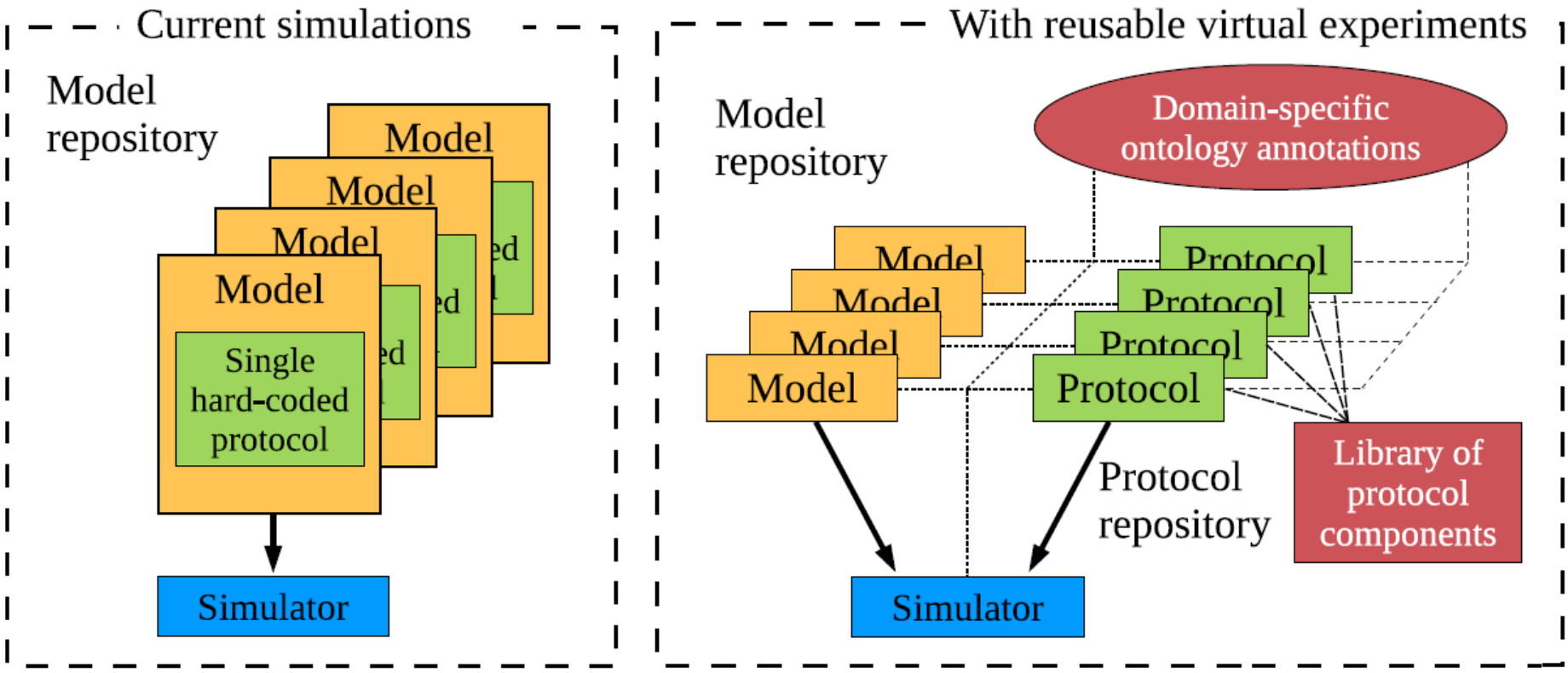
Physiome Repository

cellML
biology. math. data. knowledge.

SBML



What does the Web Lab enable?



https://chaste.cs.ox.ac.uk/WebLab

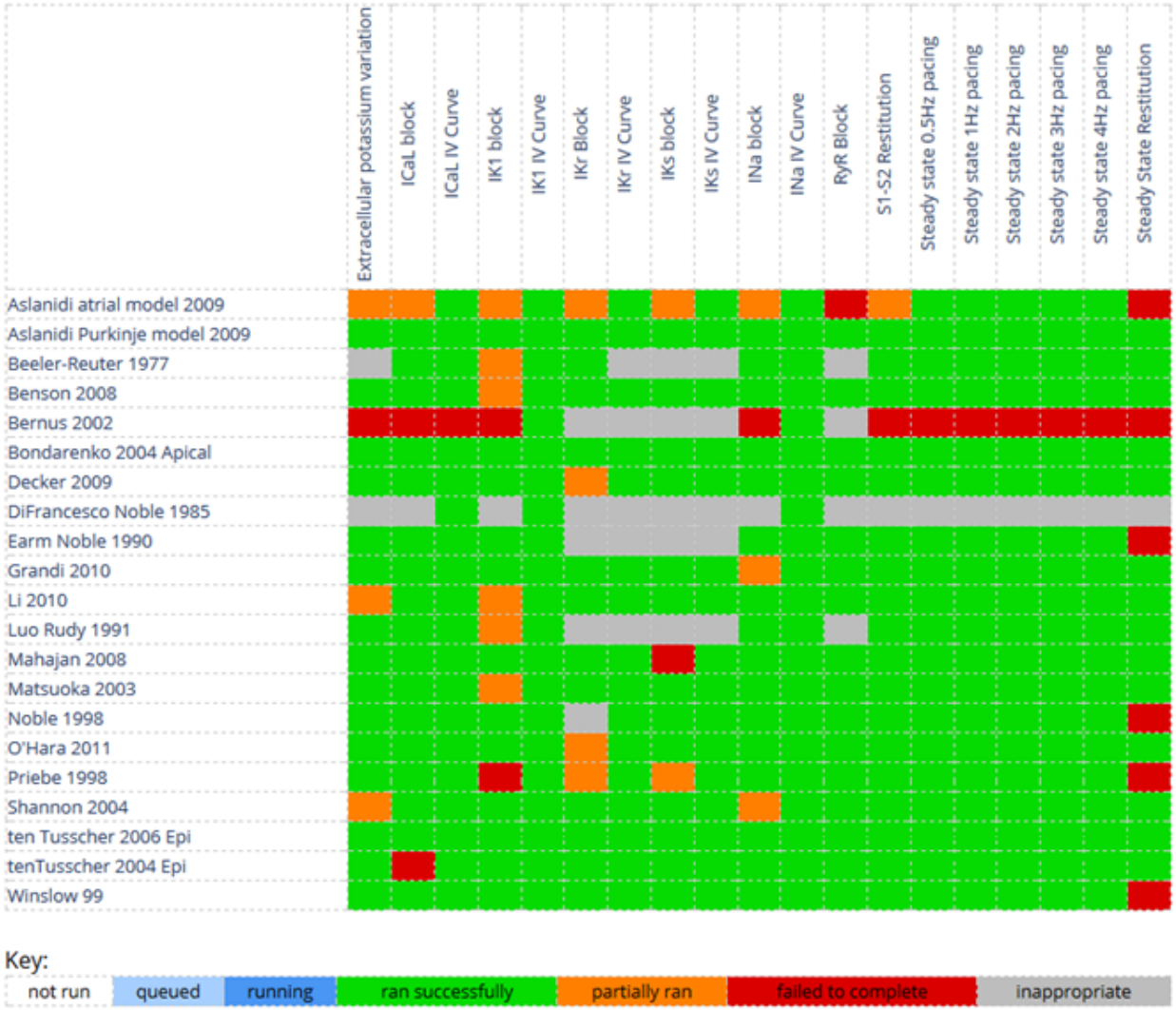
Key features summary

- Consistent application of a protocol to any model
  - Interface described at the level of biophysical concepts (ontology annotation)
  - Units conversions are all handled automatically
- Specify model inputs and outputs
  - Simulator works out which equations it needs for that simulation
- Replace components
  - For example encode your own stimulus protocol, or apply voltage clamps
- Includes all the post-processing and plotting instructions (array-based functional language)
- Able to do complex parameter sweeps, analysis, etc.

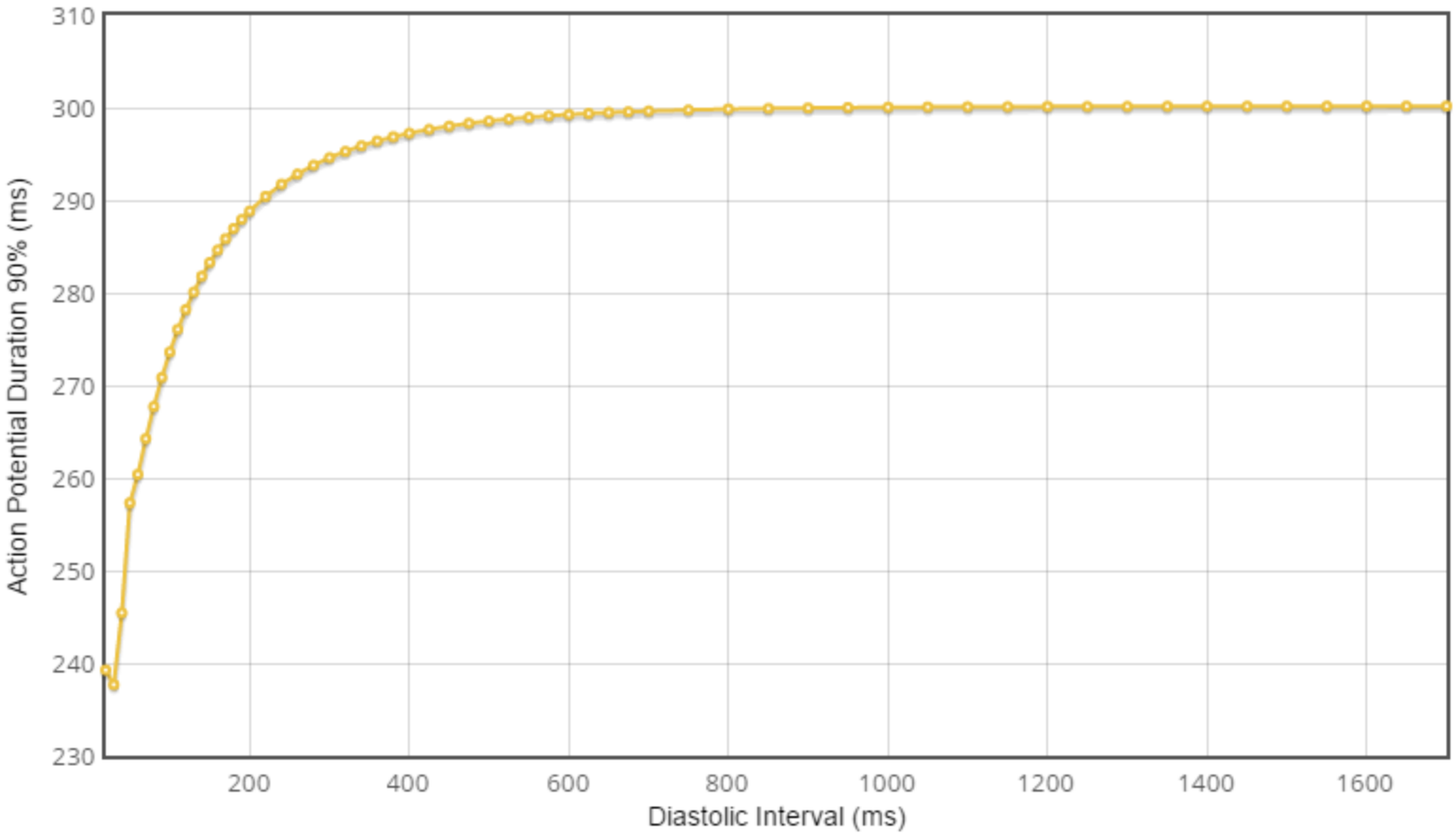
Demo

https://chaste.cs.ox.ac.uk/WebLab

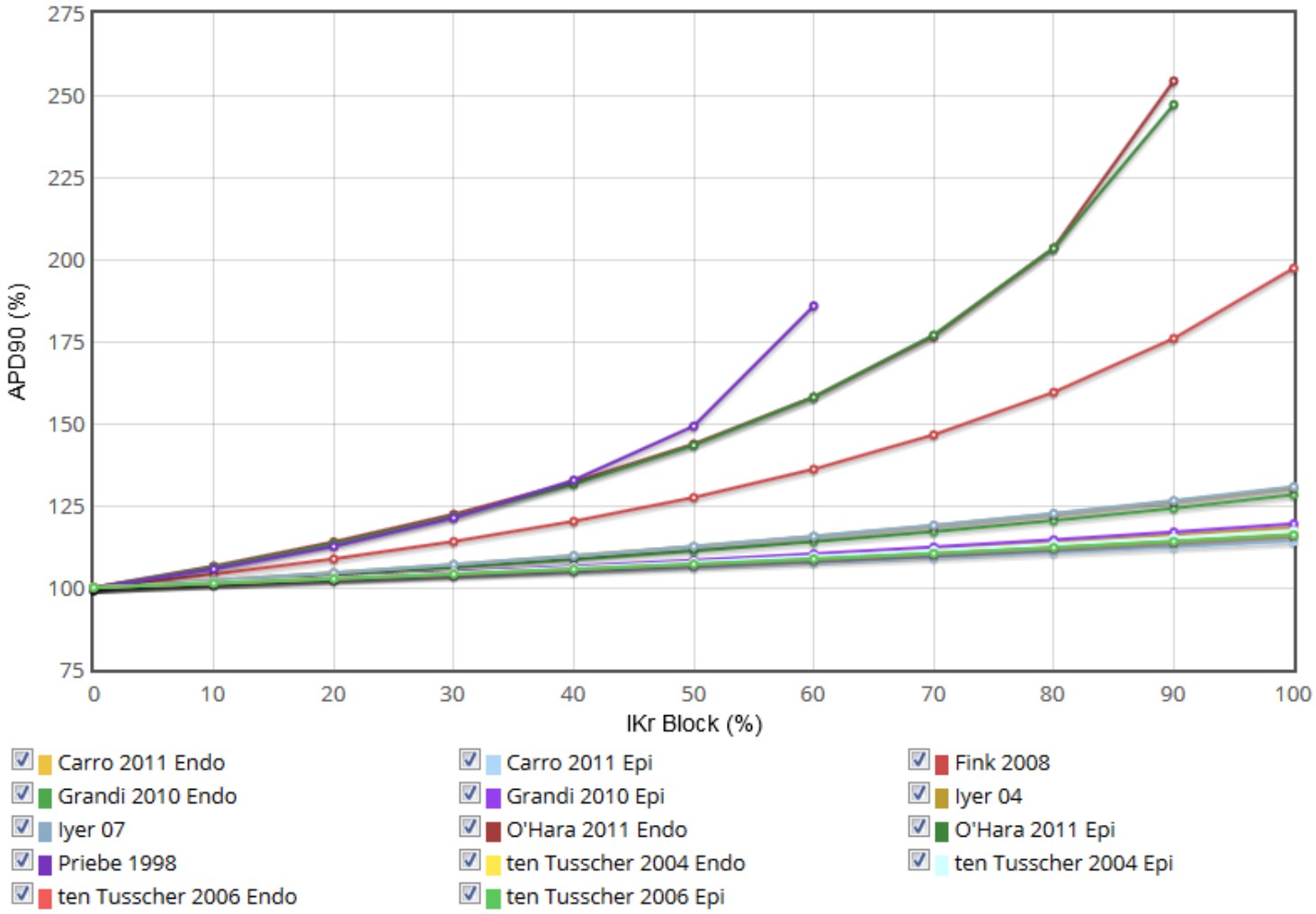
View of experiments run



Results of an experiment



Comparing experiments – drug block



Some of the technologies involved

- CellML & Combine Archive
- Python
  - Pyparsing, Amara, RDFLib
  - Numpy, pytables, numexpr
- Cython & CVODE
  - Original backend in C++
- Tomcat & JSP
- Celery & RabbitMQ
- MySQL
- Javascript & jQuery
  - rdfQuery
- Flot, Highcharts

Cython: ODE solves as fast as C

- Electrophysiology cell models are moderately complex ordinary differential equations
  - Right-hand side coded in Python => far too slow!
- "The Cython language is a superset of the **Python** language that additionally supports calling **C functions** and declaring **C types** on variables and class attributes. This allows the compiler to generate very **efficient C code** from Cython code."
- CVODE is a best-of-breed adaptive ODE solver written in C

Wrapping a C library with Cython

.pxd file:

```
cdef extern from "nvector/nvector_serial.h":
    cdef N_Vector N_VMake_Serial(long int vec_length,
                                 realtype *v_data)
    cdef struct _N_VectorContent_Serial:
        long int length
        realtype *data
    ctypedef _N_VectorContent_Serial *N_VectorContent_Serial

cdef extern from "cvode/cvode.h":
    int CV_ADAMS

    ctypedef int (*CVRhsFn)(realtype t, N_Vector y,
                            N_Vector ydot, void *user_data)
    void *CVodeCreate(int lmm, int iter)
    int CVode(void *cvode_mem, realtype tout, N_Vector yout,
              realtype *tret, int itask)
```

A Cython ODE model: .pxd file

```
cimport numpy as np

cdef class CvodeSolver:
    cdef void* cvode_mem # CVODE solver 'object'
    cdef N_Vector _state # The state vector of the model
    cdef public np.ndarray state # Numpy view of the state
    cdef public object model # The model being simulated

    cpdef Simulate(self, realtype endPoint)
```

A Cython ODE model: .pyx file

```
cimport numpy as np
import numpy as np
cimport fc.sundials.sundials as _lib

cdef extern from "Python.h":
    object PyBuffer_FromReadWriteMemory(void *ptr, Py_ssize_t size)

cdef object NumpyView(N_Vector v):
    """Create a Numpy array giving a view on the CVODE vector passed in."""
    cdef _lib.N_VectorContent_Serial v_content =
                          <_lib.N_VectorContent_Serial>(v.content)
    ret = np.empty(v_content.length, dtype=np_dtype)
    ret.data = PyBuffer_FromReadWriteMemory(v_content.data, ret.nbytes)
    return ret
```

```
    self._state = _lib.N_VMake_Serial(self._state_size,
                          <realtype*>(<np.ndarray>self.state).data)
    flag = _lib.CVodeInit(self.cvode_mem, _RhsWrapper, 0.0, self._state)
```

Numexpr: Post-proc faster than C++

- “Numexpr is a fast numerical expression evaluator for NumPy. With it, expressions that operate on arrays (like "3*a+4*b") are accelerated and use less memory than doing the same calculation in Python.”
  - No intermediates
  - Good cache utilization
  - Multi-threaded
  - Can also use the Intel Vector Math Library
- So very quick at mapping calculations over one or more n-d arrays

Timing results

Test case	ICaL Protocol	S1S2 Protocol
Original C++	197 (95)	201 (35)
Original Python	792	279
First Cython attempt	614 (583)	117 (54)
Optimised Cython	152 (125)	118 (27)
Final C++	266 (162)	204 (36)

- All times are in seconds
- Time just for simulation portion of protocol in ()

Web app: Tomcat

- Open source stack for Java-based web applications
  - Java Servlet, JavaServer Pages (JSP), etc.
- Would have been more logical to use a Python framework given the rest of the project, but this was what the intern that first developed the web interface knew!
  - So was able to get something working quickly
- Talks to:
  - MySQL database for metadata, user info, etc.
  - File system for model, protocol & result files
  - Celery via CGI
  - Javascript with AJAX + JSON

Task processing with Celery

- "Celery is an asynchronous task queue/job queue based on distributed message passing. It is focused on real-time operation, but supports scheduling as well."
- Uses RabbitMQ broker (written in Erlang) for messaging, but tasks written in Python
- Aimed at handling large numbers of quick tasks;
  Web Lab uses it for distributing long-running experiments across workers
  - And extracting protocol interface info
- Nice extras, like live monitoring on the web with Flower

Celery usage in the Web Lab

- Messages should be small
  - Pass URLs for models & protocols; experiment task downloads & unpacks these on the worker
  - Also passed a callback URL for POSTing results files
    - Callbacks are auto-retried in case front-end is busy
- Our tasks are long
  - Workers don't reserve extra tasks
  - Allow tasks to be revoked mid-run (by user action)
  - Track 'pending' and 'running' states
  - Return partial results if exceed time limit
- Optionally different workers for different users
  - At present needs manual setup
- Fairest scheduling for users still an open question

Celery code snippets

In __init__.py:

```
def ScheduleExperiment(callbackUrl, signature, modelUrl, protoUrl,
                       user='', isAdmin=False):
    """Schedule a new experiment for execution."""
    from .tasks import CheckExperiment
    # Submit the job
    result = CheckExperiment.apply_async(
        (callbackUrl, signature, modelUrl, protoUrl),
        queue=GetQueue(user, isAdmin))
    # Tell web interface that the call was successful
    print signature, "succ", result.task_id
```

In tasks.py:

```
app = celery.Celery('fcws.tasks')
app.config_from_object(celeryconfig)

@app.task(name="fcws.tasks.CheckExperiment")
def CheckExperiment(callbackUrl, signature, modelUrl, protocolUrl):
  …
```

Visualization: Flot

- A pure Javascript plotting library integrated with jQuery
- Focus on simplicity & interactivity
  - But still many options!
- Chosen because a colleague had used it previously
- Data series passed as JS arrays
  - Parsed from CSV files created by experiment runs
- For many features you have to use plugins, or even add in yourself (copied from examples)
  - Graph legend with ability to turn traces on & off
  - Zoom & pan with ‘reset’ button
  - Hover over point for details tooltip

Visualization: Highcharts

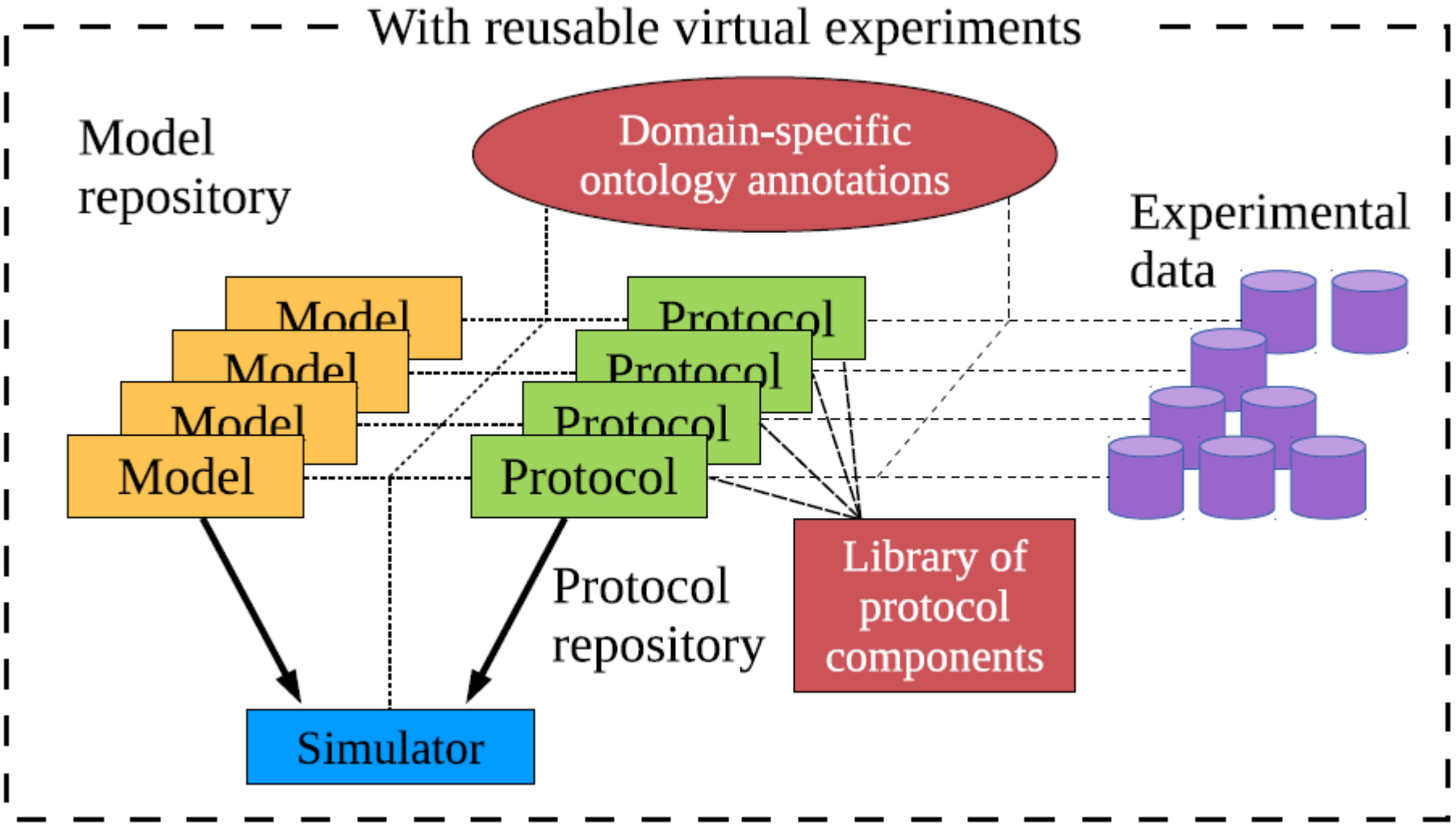
- Commercial product but free for non-commercial use, and open source
- Wanted to find something that required less customisation
  - Has built-in hover, legend & zoom, for instance
- May be harder to customise if you want to though!
- API is similar to Flot, but various minor differences in naming & options structure

Data & Metadata in Javascript

- Currently serve CSV to the front-end
- Would like to move to HDF5, but no Javascript library?
- We use down-sampling for plots to speed up rendering

- Metadata encoded in RDF/XML within models
- Created a Javascript drag & drop model annotator
- Javascript RDF/XML support is patchy!

The future of Web Lab



Final thoughts

- It's fun to have a complex project on which you can try out different technologies ☺
- Balance between choosing a 'best' solution and going with something you can get working in a reasonable time
  - Particularly for web apps, which framework is 'best' changes rapidly!
- Sometimes it's best to throw away what you have and start afresh – learn from your prototype's mistakes
- Comparing different implementations of numerical code is (very) hard

Acknowledgments

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  - David Gavaghan
  - Denis & Penny Noble


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