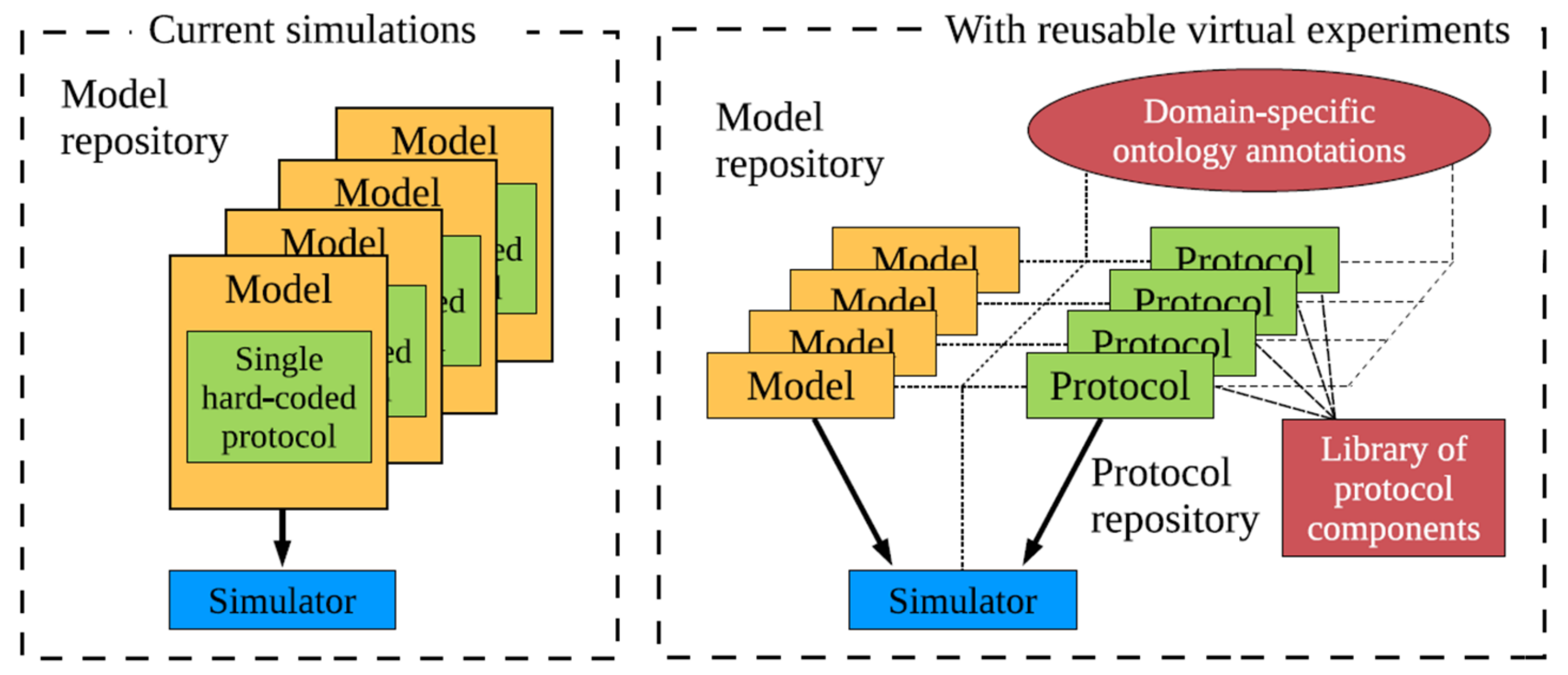


Introduction

Thanks to efforts such as the Physiome repository we can now easily share the equations and parameters of a mathematical electrophysiology model.

But at the moment we can't easily share information on what simulation we did with it.



By separating the model from the experiment that is performed, and post-processing that is applied, we can also make the experiment reproducible and shareable.

We believe this is the first step towards systematic model validation, and fully reproducible studies.

Ingredients:
Model – defined in CellML.



Protocol – defined in our own extensions to SED-ML.



Link – our own new metadata annotations.

An example protocol definition

```

inputs {
  pacing_period = 1000 # ms
  num_inner_paces = 1 # How many paces to run between comparing state variables
  max_paces = 10000 # Give up at this point
  norm_threshold = 1e-6 # Applied to p1 norm of state variable differences
}

import std = "basiclibrary.txt"
library {
  max_inner_runs = MathML:celling(max_paces / num_inner_paces)
}

tasks {
  # Get the model to steady-state (if possible)
  simulation outer = nested {
    range paces units dimensionless while outer:norm_of_differences[-1] > norm_threshold && paces < max_inner_runs
    nests protocol "singlepace.txt" {
      num_paces = num_inner_paces
      pacing_period = pacing_period
      select output norm_of_differences
      select output final_state_variables
    }
  }

  # Run a single pace in detail, to see what it looks like at steady-state
  simulation detail = tncourse {
    range time units ms uniform -10:(pacing_period * num_inner_paces):10
  }
}

post-processing {
  num_nested_runs = outer:norm_of_differences.SHAPE[0]
  num_paces = num_nested_runs * num_inner_paces
  pace_count = [count for count in 0:num_nested_runs] # Used for plotting
  found_steady_state = num_paces < max_paces
  steady_state_variables = outer:final_state_variables[-1]
  pace_final_state_variables = std:transpose(outer:final_state_variables)
  detailed_state = std:transpose(detail:state_variable)
}

outputs {
  num_paces units dimensionless "The number of paces required to get to an approximately steady state"
  steady_state_variables units mixed "The state variables at an approximately steady state"
  found_steady_state units boolean "Whether we found a pseudo-steady-state, or gave up"
  pace_final_state_variables units mixed "State variables at the end of each pace"
  num_inner_paces units dimensionless "The number of paces per check of state variables"
  pace_count units dimensionless "Paces"
}

norm_of_differences = outer:norm_of_differences "Norm of the change in state variables over each 'pace'"
detailed_time = detail:time "Time"
detailed_state = detail:state_variables "State variables over the final 'pace'"
detailed_voltage = detail:membrane_voltage "Transmembrane potential"
}

plots {
  "final pace voltage" using lines { detailed_voltage against detailed_time }
  "Progress towards steady state" { norm_of_differences against pace_count }
  "State variables at each pace end" using lines { pace_final_state_variables against pace_count }
}

```

Web Lab Features

<https://chaste.cs.ox.ac.uk/FunctionalCuration>

The first place you have been able to view basic model properties like action potential shape.

Compare different models under a protocol, a model under different protocols, or any combination.

Units conversions are handled automatically, and models are simplified if equations are not required for specified outputs. e.g. individual current IV curves.

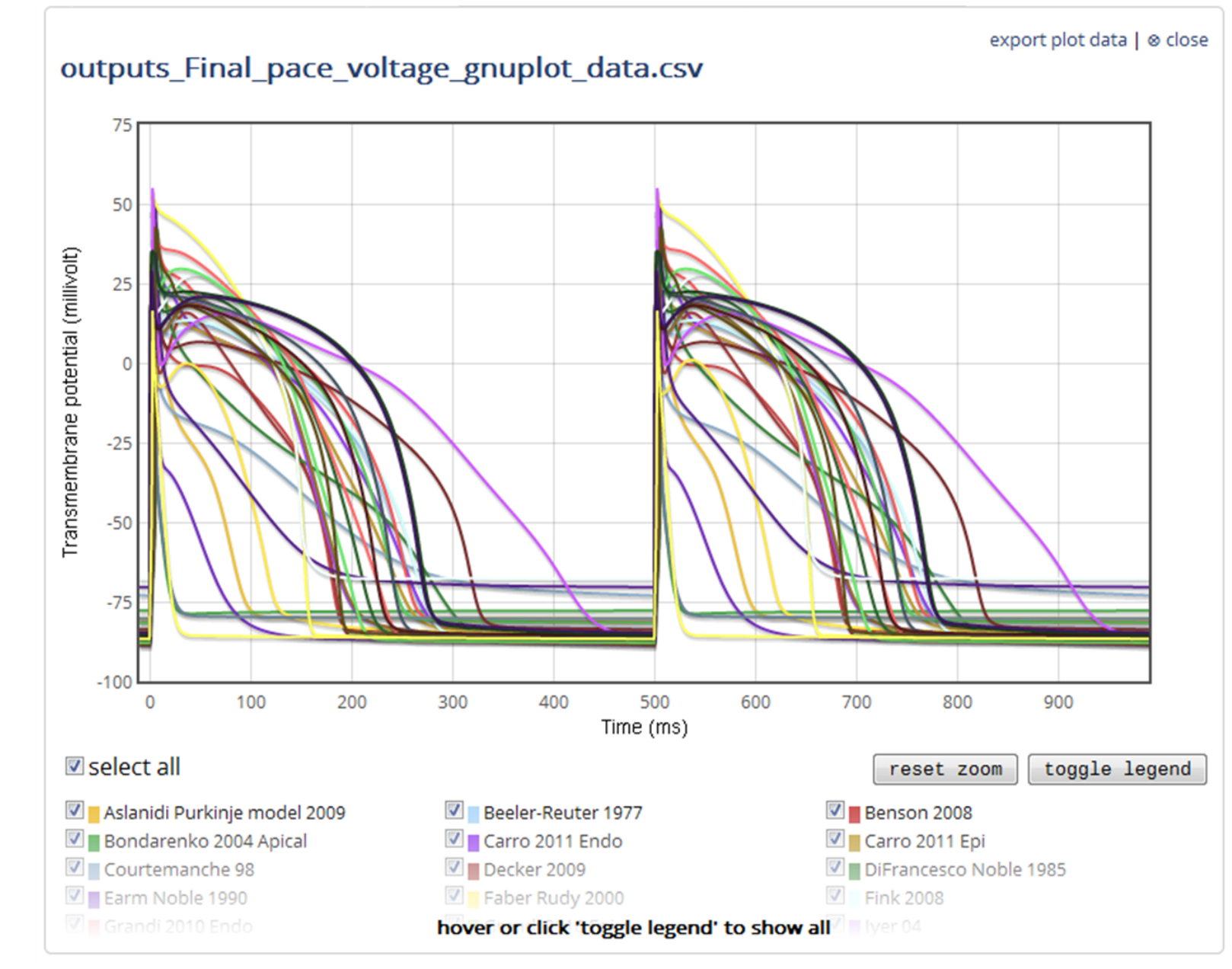
The Web Lab is already useful for selecting models that exhibit certain behaviours for particular simulation studies (e.g. restitution curves).

We have also been able to identify and correct bugs in CellML encodings by attempting to reproduce original publication figures.

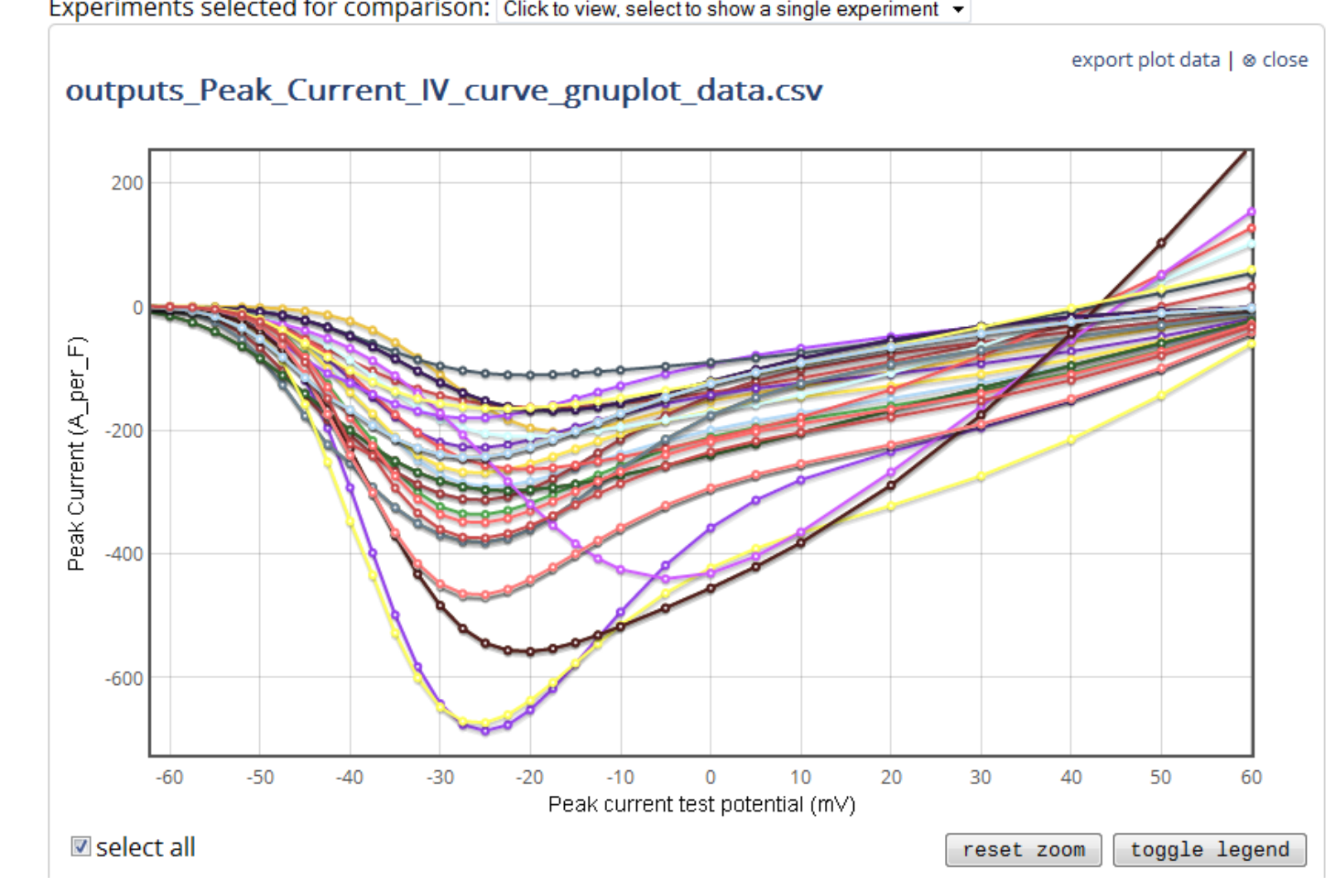
All versions of models and protocols are stored and can be compared.

Comparison of Models

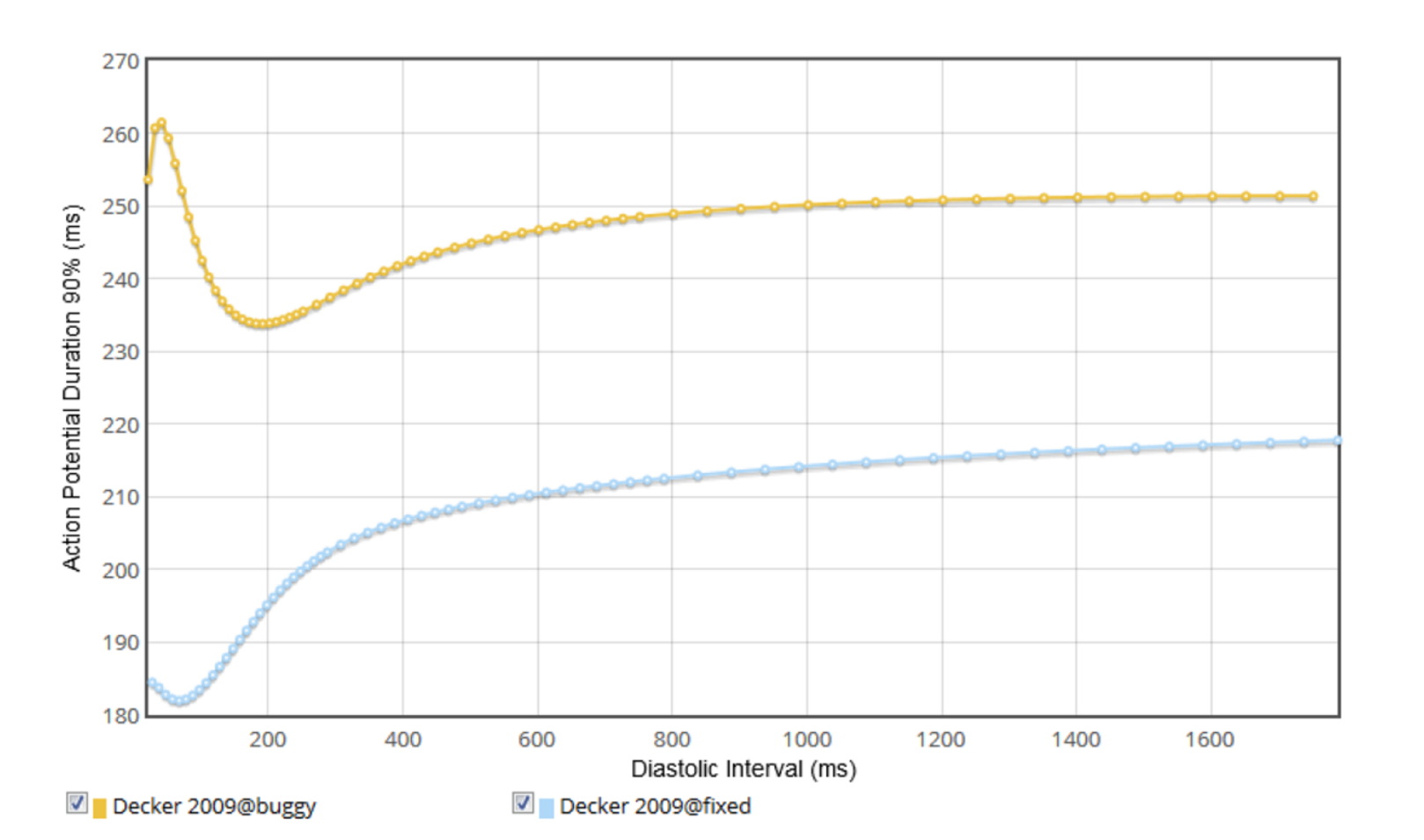
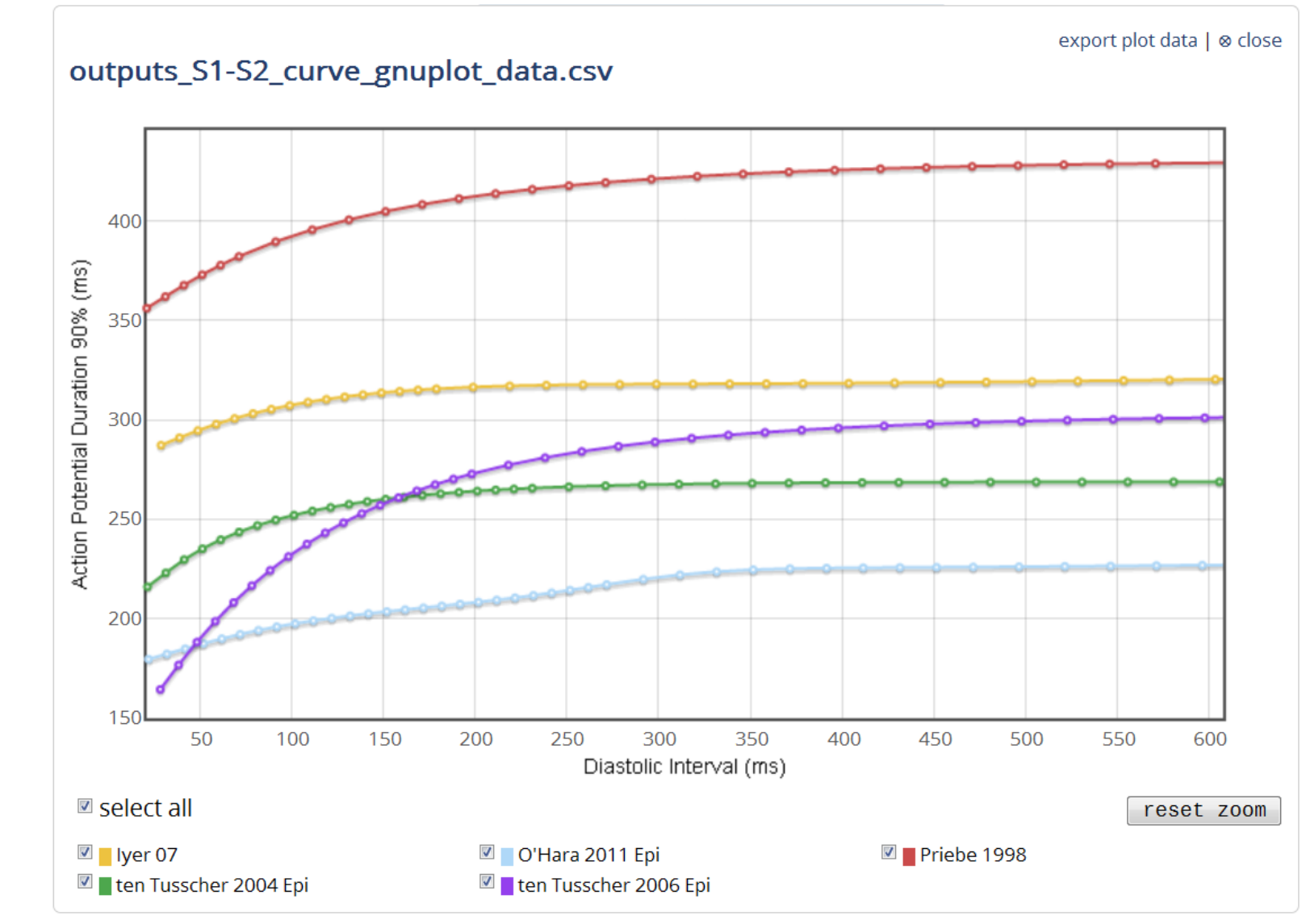
Steady state action potentials



Fast sodium current peak IV curves



S1-S2 restitution curves

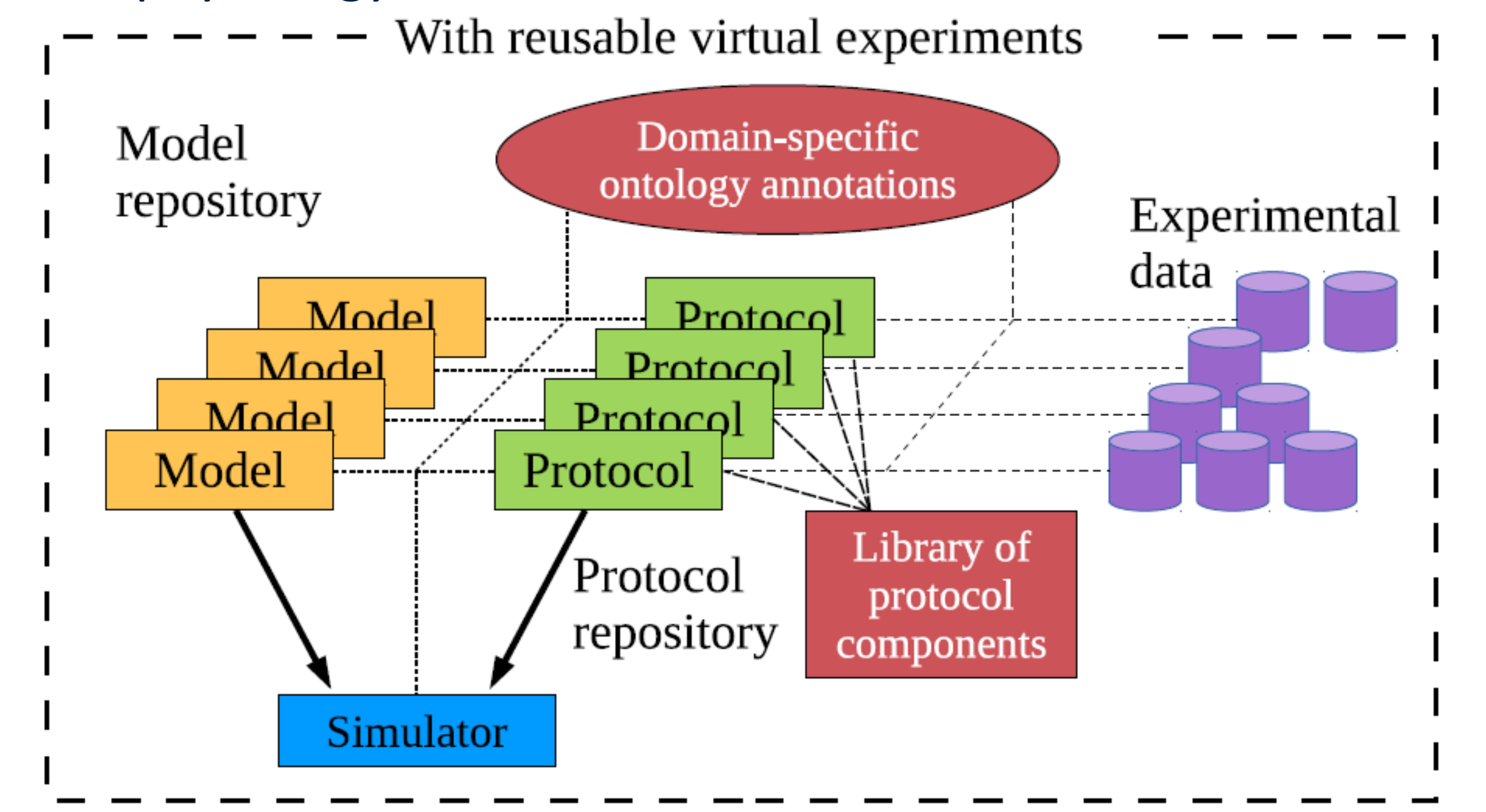


Future Work

You can already upload and share your own models and protocols, and test against any existing ones at the click of a button.

Future tasks include: development of a full ontology (rather than simply metadata tags); annotation of all cardiac electrophysiology models in CellML repository; development of a protocol editing GUI; collection of wet-lab data. Collaborations welcome!

We aim to couple the protocol descriptions to wet lab data, and parameter fitting algorithms, to allow everything necessary to create a model to be shared and stored for re-use to dramatically reduce the barrier to further development of electrophysiology models.



Further reading

- Cooper *et al.* *A call for virtual experiments: Accelerating the scientific process.* PBMB (2014) 117(1), 99-106.
- Cooper *et al.* *High throughput functional curation of cellular electrophysiology models.* PBMB (2011) 107, 11-20.

Acknowledgements

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