CellML 1.1 modularity

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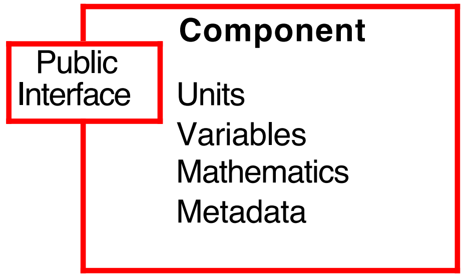
CellML

- CellML is designed to support the definition and sharing of models of biological processes.
- CellML includes information about:
  - Model structure (how the parts of a model are organizationally related to one another);
  - Mathematics (equations describing the underlying biological processes);
  - Metadata (additional information about the model that allows scientists to search for specific models or model components in a database or other repository).
- A public repository of over 500 published signal transduction, electrophysiological, mechanical, and metabolic pathway processes is available at *http://models.cellml.org/*

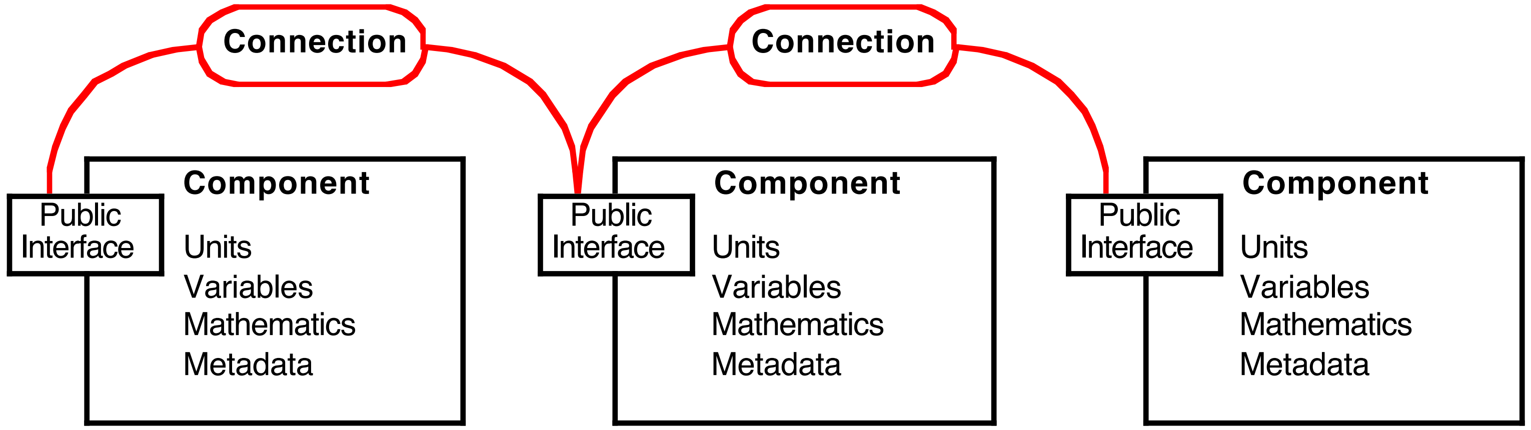
CellML components

- CellML has a simple structure based upon connected *components*.
- Components abstract concepts by providing well-defined interfaces to other components.
- Components encapsulate concepts by hiding details from other components.



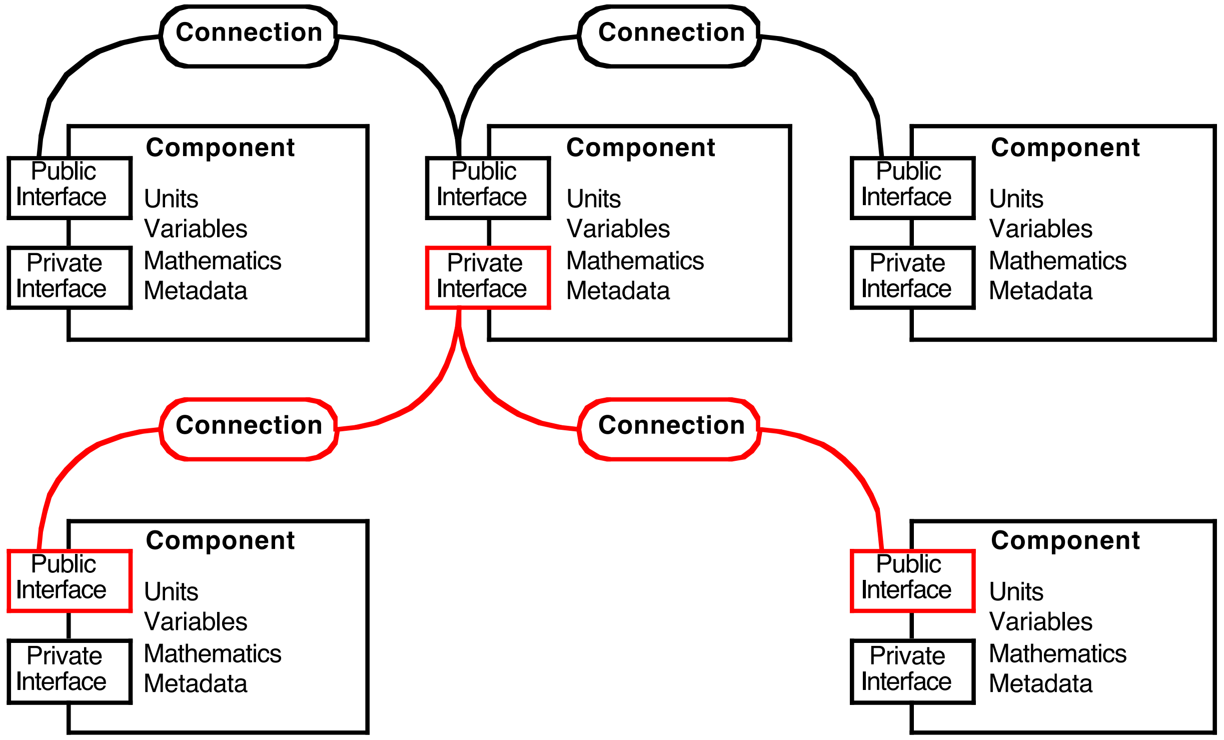
CellML connections

- *Connections* provide the means for sharing information by associating variables visible in the interface of one component with those in the interface of another component.
- Consistency is enforced by requiring that all variables be assigned appropriate physical *units*.



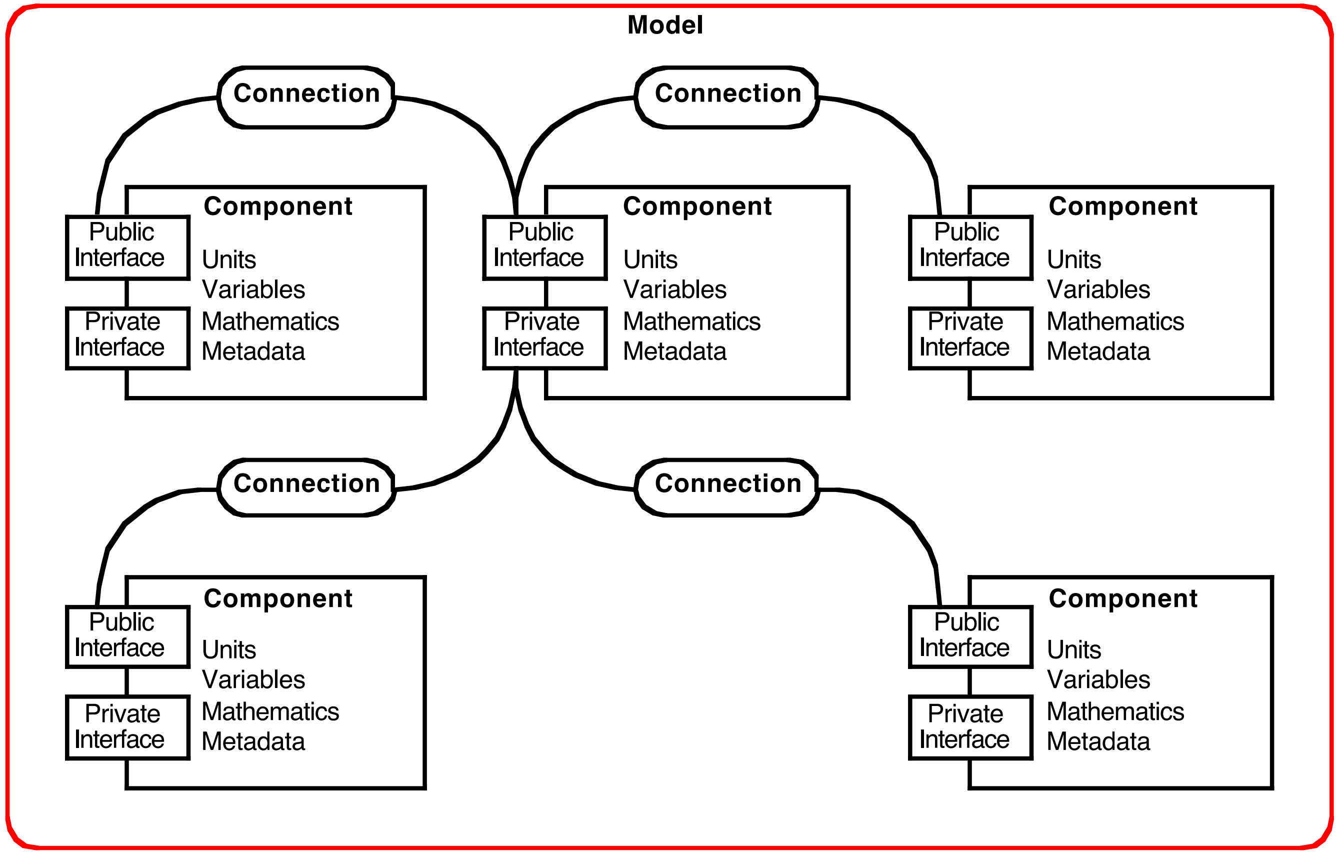
CellML encapsulation

- Encapsulation hierarchies are enabled using *private interfaces*.



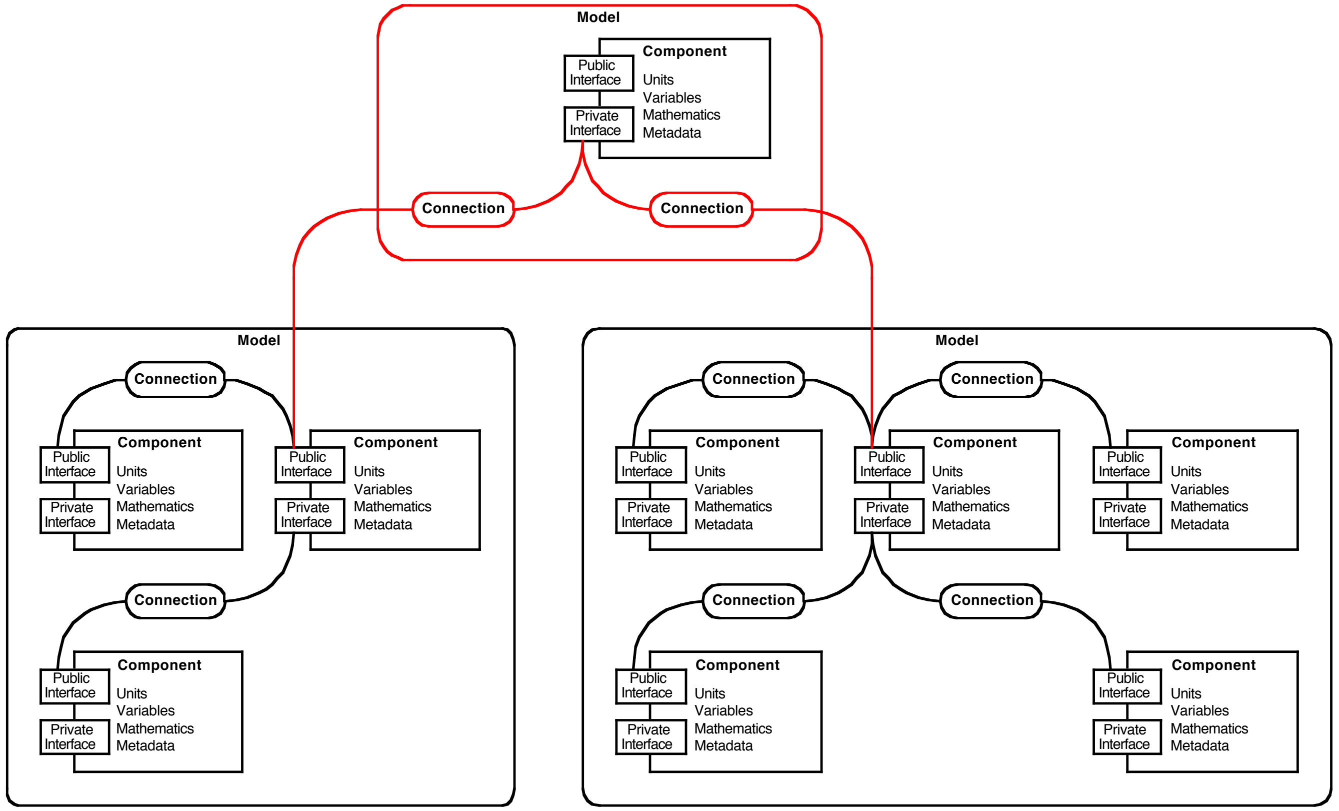
CellML model

- A *model* is the root element for a CellML document. It is a container for components, connections, units, and metadata.



CellML import

- Model reuse is enabled by the *import* element.
- New models may thus be constructed by combining existing models into model hierarchies.



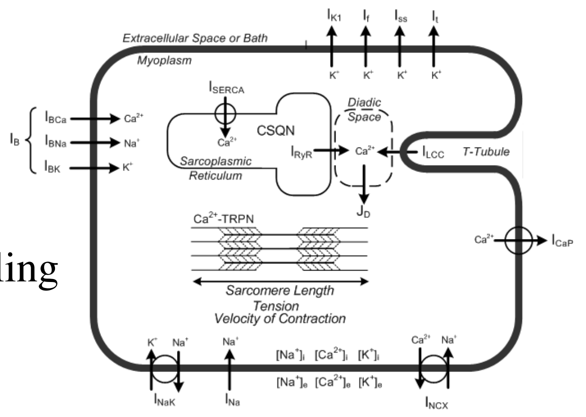
Model libraries

- Model reuse encourages the creation of model libraries.
- This is possible in CellML because there is no distinction between models as stand-alone entities and models as templates.
- Every import creates a new instance of the imported model in the importing model.
- The same model can be imported multiple times to create separate instances (with distinct identifiers) within the importing model.

Model libraries

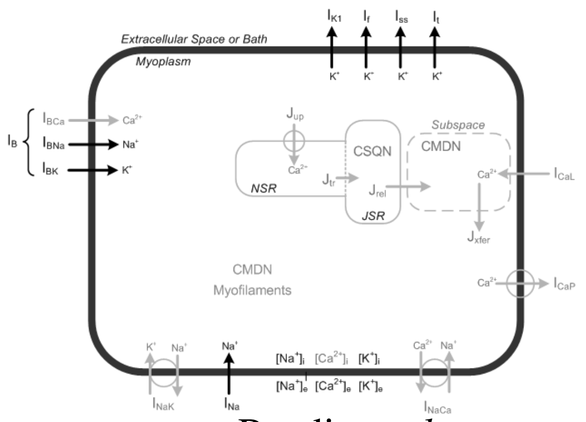
- Obvious candidates for reuse are existing CellML 1.0 models available in the model repository.
- Other candidates are the decomposition of existing models by identifying reusable generic (sub)models.
- These generic models are then formulated as new library models, making them available as basic building blocks for import into larger models.
- Useful generic models include collections of:
  - units (complicated combinations, non-SI definitions)
  - constants (codata fundamental physical constants)
  - processes (integrators, reactions, rate relations, ion channels, …)
- Sometimes difficult to balance genericity versus conciseness.

Combine models using CellML import



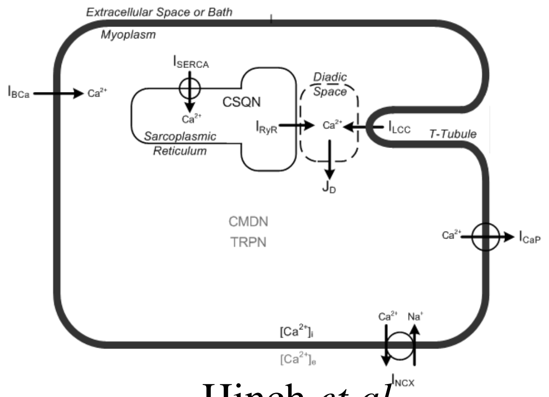
Extracellular Space or Bath
Myoplasm
I_{K1} I_f I_{ss} I_t
K^+
I_{SERCA}
CSQN
Diadic Space
Sarcoplasmic Reticulum
I_{RyR}
I_{LCC}
T-Tubule
J_D
I_B I_{BCa} I_{BNa} I_{BK}
Ca^{2+}-TRPN
Sarcomere Length
Tension
Velocity of Contraction
I_{CaP}
$[Na^+]_i$ $[Ca^{2+}]_i$ $[K^+]_i$
$[Na^+]_e$ $[Ca^{2+}]_e$ $[K^+]_e$
I_{NaK} I_{Na} I_{NCX}

Terkildsen *et al*.
Integrated model of e-c coupling

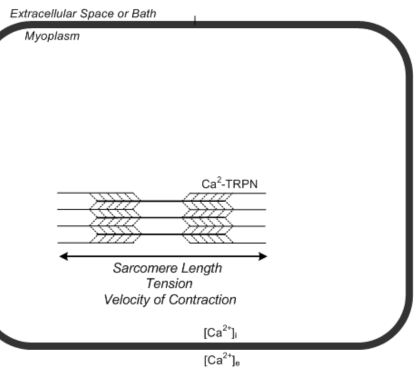


Extracellular Space or Bath
Myoplasm
I_{K1} I_f I_{ss} I_t
I_B I_{BCa} I_{BNa} I_{BK}
J_{up}
CSQN
NSR
JSR
J_{tr} J_{rel}
Subspace
CMDN
I_{CaL}
J_{xfer}
CMDN
Myofilaments
I_{CaP}
$[Na^+]_i$ $[Ca^{2+}]_i$ $[K^+]_i$
$[Na^+]_e$ $[Ca^{2+}]_e$ $[K^+]_e$
I_{NaK} I_{Na} I_{NaCa}

Pandit *et al*.
cardiac action potential



Hinch *et al*.
Ca-induced Ca release



Niederer *et al*.
myofilament mechanics

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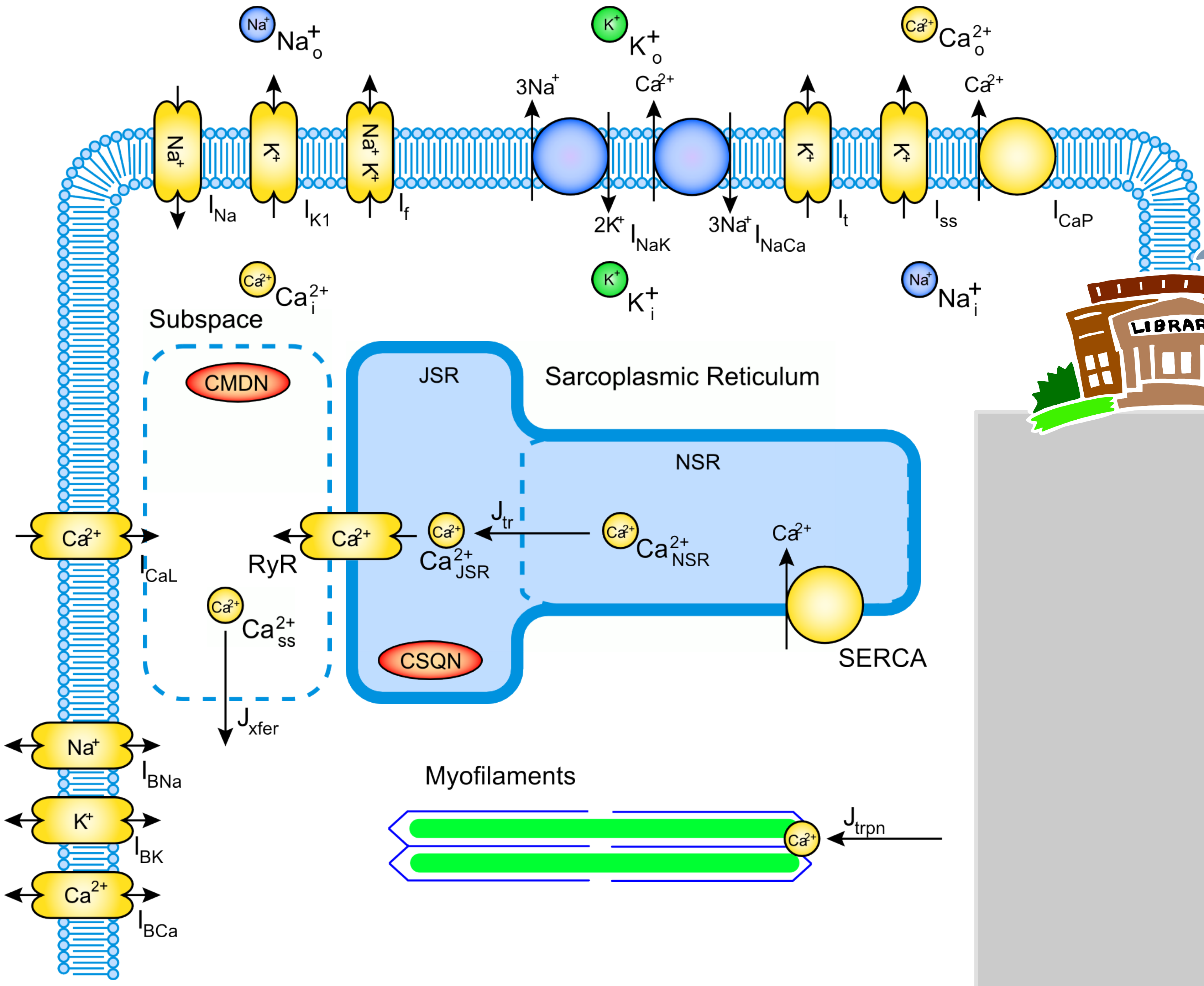
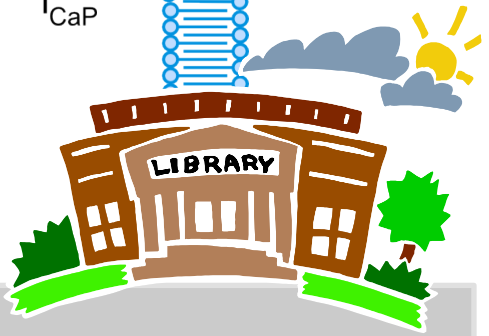

Na^+_o
K^+_o
Ca^{2+}_o
$3Na^+$
Ca^{2+}
Ca^{2+}
Na^+
K^+
$Na^+ K^+$
K^+
K^+
I_{Na}
I_{K1}
I_f
$2K^+$
I_{NaK}
$3Na^+$
I_{NaCa}
I_t
I_{ss}
I_{CaP}
Ca^{2+}_i
K^+_i
Na^+_i
Subspace
CMDN
JSR
Sarcoplasmic Reticulum
NSR
Ca^{2+}
I_{CaL}
Ca^{2+}
RyR
J_{tr}
Ca^{2+}_{JSR}
Ca^{2+}_{NSR}
Ca^{2+}
Ca^{2+}_{ss}
CSQN
SERCA
J_{xfer}
Na^+
I_{BNa}
K^+
I_{BK}
Ca^{2+}
I_{BCa}
Myofilaments
J_{trpn}

LIBRARY

Best practice

- Most useful non-trivial library components describe clearly identifiable biophysical processes.
- Sarala Wimilaratne has given several examples of this approach in her PhD thesis on CellML model visualisation (Cooling 07 GCPR cycle, Hodgkin-Huxley 52, Nobel 62).
- We are compiling a list of best-practice examples based on the experience gained through the process of model decomposition.
- This work is still in its early stages – there is still much to be learned about which approaches offer the best long-term benefits. Mike Cooling has a poster in the ICSB conference.
- Others in this session will discuss the new tools that have been built to facilitate model reuse.

Best practice

- Put reusable mathematics in separate components, and use <*import*>s to instantiate these for use where appropriate.
- Use '*_delta*' components to extensibly connect multiple fluxes to species of interest.
- Use separate conversion components for connections where applicable.
- Build coarse-grained components from aggregations of finer-grained, biologically atomic components.
- Define <*units*> at the lowest level possible, <*import*>ing into higher level components as necessary.
- Separate out all parameter values into one or more non-mathematical CellML documents.
- Universal constants should be <*import*>ed from a non-mathematical CellML document (a standard based document on [UC] is recommended).
- If encapsulating, expose all potentially useful values using *public_interface*="*out*".