Meeting Minutes 28 November

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1　Introduction

Melanie donated some of her holiday hours while in Auckland to meet with Warren and Poul and discuss some new requirements for the specification of qualitative pathway models and propose improvements to the current system. The metadata part of the specification, which Melanie had developed in October, was then given a close reading by the Auckland team (who had already read it carefully a number of times, but pretended they hadn't for Melanie's benefit.)

2　More Qualitative Pathway Modelling

2.1　Requirements

Previously, Prasad, Kam and Melanie at Physiome Sciences, Inc. had spent considerable effort persuading Poul, David and Warren at Auckland that the specification of qualitative pathway models using a non-mathematical notation was needed (see the September 22 Meeting Minutes[1]). As Melanie worked on the CellML description of the EGF Activation Pathway example some limitations of the method developed and presented in that document became obvious, and this was summed up neatly by Melanie in an e-mail on November 22.

> There is no way to indicate in the **`<reaction>`** element that a reaction is bidirectional. This is actually a problem related to the one Bob Phair raised about autocatalysis, substrate inhibition and other cases where one chemical species plays more than one role in a reaction. We need a way to indicate that a chemical species participates in more than one way in a reaction. Bidirectional reactions could then be indicated simply by labeling the appropriate variables as both reactants and products.

The problem raised by Bob Phair involved situations where a single species is both reactant and catalyst in the same reaction. In a reversible reaction, these species might only play one of these roles in a single direction: for instance, an enzyme typically catalyses a reaction in the forward direction, but not the backward direction. A part of the EGF activation pathway model where this occurs is shown in Figure 1.

2.2　Solutions

After a couple of iterations, Melanie and Warren had arrived at the scheme shown in Figure 2. In this scheme, the **`<reaction>`** element has a boolean (i.e. may have values `"yes"` or `"no"`) attribute **`reversible`**, where the absence of the attribute indicates the default value of `"yes"`. Each variable reference (the **`<variable ref>`** elements) can now contain multiple **`<participation>`** elements (participation was formerly an attribute on the **`<variable ref>`** element). The **`<participation>`** element contains a **`participation`** attribute where the actual type of reaction participation is defined for the current variable. The **`<participation>`** element may also contain a **`direction`** attribute which

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[1] http://www.cellml.org/private/progress reports/20000922 meeting minutes.html
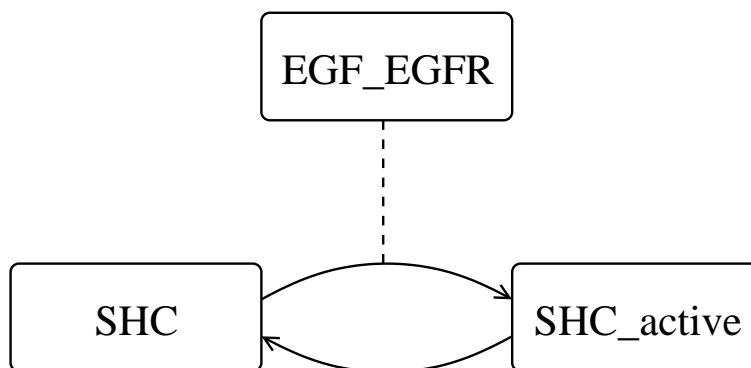
FIGURE 1: A subpathway from the EGF activation pathway model where a species acts as a reactant in one direction only of a reversible reaction.

can be used to indicate that the participation of a species in the reaction is only in a single direction for a reversible reaction.

```
<reaction reversible="yes">
  <variable_ref name_ref="EGF_EGFR">
    <participation direction="forward" participation="catalyst" />
  </variable_ref>
  <variable_ref name_ref="SHC">
    <participation participation="reactant" />
  </variable_ref>
  <variable_ref name_ref="SHC_active">
    <participation participation="product" />
  </variable_ref>
</reaction>
```

FIGURE 2: A possible scheme for specifying qualitative pathway models which is capable of handling reversible reactions and multiple roles of a variable in a reaction. This particular example is based on the sub-pathway shown in Figure 1.

The **direction** attribute may take the values "forward" and "reverse", and may only be present on **<participation>** elements that are inside a reversible reaction. The absence of a **direction** attribute inside a reversible reaction indicates that the variable referenced in the enclosing element participates in the specified way in both directions. The **participation** attribute is required on all **<participation>** elements and may take one of the following values:

- reactant
- product
- catalyst
- inhibitor
- modifier

Poul had some sensible objections to this proposal. First of all, in the cases where a mathematical formulation of the reaction process was also specified, we would have two potentially inconsistent representations of the same information. Warren believed however that the primary purpose of the **`<reaction>`** element is to allow the concise intuitive definition of qualitative pathway models and to provide rendering information (i.e., to allow software to construct diagrams like the one in Figure 1). As it would be extremely difficult to construct useful diagrams from purely mathematical descriptions of reactions, something like the **`<reaction>`** element is going to be pretty much necessary in any case to go alongside mathematics.

Poul was also concerned about the gradual addition of information of mathematics to qualitative models, wanting as he put it a "*graceful transition*". We could say that the model behaviour is always determined by mathematics even in the presence of a **`<reaction>`** element if it exists, and the representation of the model is always determined by the **`<reaction>`** element, even in the presence of math. However we should probably explicitly specify some rules governing this behaviour. Given that a modeller could well put an entire pathway model inside a single **`<component>`** element by including numerous **`<reaction>`** elements inside it, we might need some way of indicating which reactions are to be determined from math and which are to be determined from the qualitative information. (Someone should probably modify the simple pathway model to have two reactions in one component as a test case for this.)

2.3   To-Do List:

So we're not quite done in this area. We still need to consider the following:

1. **Do we currently have enough to completely specify qualitative models?** Is the scheme presented in Figure 2 sufficient to perform the kind of analysis which people might want to do with qualitative models. (For example, what happens when we remove species A?)

2. **A specification for the graceful transition from qualitative to quantitative models.** As mathematical information is added to a qualitative model, is it currently possible for processing software to work out which information is relevant?

3. **Are we worried about multiple reactions in one component?** In developing the initial **`<reaction>`** element scheme, there was some crazy talk about allowing only one reaction per component. Is there going to be more of this madness?

3   Metadata Specification Review

A close reading through the metadata specification revealed that Warren and Poul had pretty much no clue about RDF, and so they needed to do some more research before they could really offer up any useful criticism. They did however have a few suggestions about syntax changes.

Warren's main concern was the amount of XML needed to specify even the simplest piece of metadata — in particular the need for the **`<rdf:RDF>`** and **`<rdf:Description>`** elements on every piece of metadata. This would make it extremely painful to insert small pieces of metadata such as last-modified dates and annotations by hand into a CellML model.