

A comparison of cellML and sbML using a model of hormone
induced glycogenolysis in hepatocytes

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1 Abstract

Systems Biology aims to produce coherent models of biological systems that are made from many interacting components. Individually each component may be well understood with accepted behavioural models. However, these models are often represented in different software languages and on different computer platforms. To integrate these models a neutral exchange format is needed. cellML and sbML are XML based neutral exchange languages for modeling cellular processes. This essay is a comparison of the two languages. The experience of encoding a model of hormone induced glycogenolysis in hepatic cells is the basis for the comparison.

2 Introduction

Sharing biological information is increasingly important in today's scientific community. Day-to-day science is progressively becoming a global activity as initiatives such as the UK's 'e-science' programme illustrate [E-science()]. The key message of the last meeting of the World Summit on the Information Society (WSIS) was that access to scientific information should be more easily and freely available to promote innovative research [Mantell(2003)]. New areas of biological research such as 'Systems Biology' are inherently integrative their approach to answering biological questions and require a suitably flexible format for exchanging information between constituent components of the studied system.

This essay focuses on the need for a neutral exchange format for biological models in Systems Biology. Systems Biology is concerned with modeling complex systems composed of many interacting components. An example of this is an *in silico* model of the liver which must integrate a diverse collection of models on an equally broad range of length scales [Beacon()]. Individually each component may be well understood with accepted behavioral models. However these component models are likely to be represented in different languages and in different software environments, so integrating a particular component could involve a complex translation process. A neutral exchange format aims to eliminate the need for the translation by facilitating the use of multiple software tools without requiring the model to be recoded, and ensures the longevity of a particular model beyond the lifetime of the software it is represented in.

A neutral exchange format must be suitably flexible; it must be able to store a variety of information in sufficient detail, with structures that enhance rather than constrain the information stored. The format should also support meta-information allowing the representation to be comprehensible without the pre-requisite of external information. XML (extensible markup language) is a commonly used platform-independent text-based markup language for storing structured information. sbML and cellML are languages that use the generality of XML to provide a neutral exchange format for modeling cellular processes. Both languages are gaining acceptance in the biological modeling community. In this essay the languages are reviewed and compared.

A model of glycogenolysis in hepatic cells and its control by extra-cellular hormones is used as a test model to compare sbML and cellML. Hepatic glycogenolysis is used because the cellular processes are comparatively well understood and are relatively modular. The ease of encoding each module and then sharing information between the modules is assessed.

Glycogenolysis (and the reverse process glycogenesis) is the conversion from glycogen into glucose. Glycogen is a polysaccharide used in most mammalian cells as a store for glucose. In most cells glycogen is broken down as required and the resulting glucose is converted to glucose-6-phosphate and used as a metabolic fuel for glycolysis, an important process in cellular energy production.

In the liver, glycogen is primarily stored as a reservoir of glucose for extra-hepatic cells. After glycogenolysis, the resulting glucose is not converted to glucose-6-phosphate but is instead exported into the blood stream for use by extra-hepatic cells. The level of hepatic glycogen varies considerably with feeding condition; it is estimated that during the first day of starvation between 40-80% of glucose production is due to hepatic glycogenolysis. The rates of hepatic glycogen synthesis and degradation are strongly influenced by the concentration of certain hormones in the blood; glycogenolysis accounts for nearly all of the response to glucagon (a hormone that raises the glucose concentration in the blood) and insulin (a hormone that lowers glucose concentration). The importance of glycogenolysis compared to gluconeogenesis (the production of glucose from constituent molecules such as ATP) is illustrated by the speed that hypoglycaemia (abnormally low glucose level) occurs in individuals with deficient glycogen synthase (the primary enzyme for glycogenolysis). [Bollen et al.(1998)Bollen, Keppens, and Stalmans].

The hepatic-enzymes responsible for glycogen synthesis and degradation are specially adapted to allow hepatic cells to regulate the glucose levels in the blood. Glucose is transported across the hepatic cell membrane by the glucose transporter enzyme (GLUT). GLUT does not respond strongly to insulin and is not rate limiting in glucose transport. This means that the glucose concentration in the blood is the same as in the liver which allows hepatocytes to monitor blood glucose levels.

The primary conversion from glucose to glycogen and vice-versa is facilitated by glycogen synthase and glycogen phosphorylase respectively. These two enzymes respond strongly to phosphorylation; synthase is deactivated by phosphorylation and phosphorylase is activated. This is illustrated in figure 1.

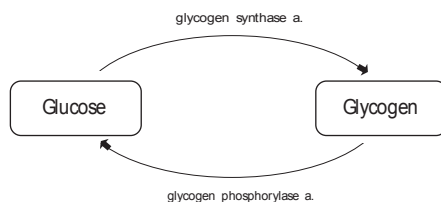


Figure 1: glucose-glycogen conversion cycle

The phosphorylation rate in hepatocytes is sensitive to the blood glucose concentration and also to the levels of extra-cellular hormones such as glucagon, insulin and adrenaline. The signalling and control mechanisms induced by adrenaline and glucagon that increase the rate of glycogenolysis are described in the next section. Models of the mechanisms are then presented; and then the models are used to facilitate a comparison between cellML and sbML.

3 Phenomenology of glycogenesis control

3.1 G-protein linked receptors

The initial signalling process is regulated by g-proteins. G-proteins are trimeric GTP binding proteins. The subunits are labelled $\alpha\beta\gamma$ with the α -subunit weakly bound to the strongly coupled $\beta\gamma$. In the inactive form, the α -subunit is bound to GDP. G-protein linked receptors are cell surface receptors and are specific to a particular agonist.

When an extra-cellular ligand such as adrenaline or glucagon binds to an a g-protein linked receptor (adrenaline binds to a β -adrenergic receptor), the receptor changes the conformation of its intra-cellular

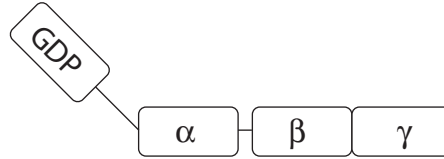


Figure 2: G-protein structure

g-protein receptor, allowing an inactive g-protein to bind. The receptor activates the bound g-protein, causing it to replace the bound GDP with GTP. The α -subunit then dissociates from the $\beta\gamma$ section and can activate other secondary signalling proteins.

A bound receptor is thought to be sensitive to desensitization. Desensitization occurs when an arrestin binds to a receptor, causing it to be removed from the plasma membrane, internalised and eventually recycled back onto the plasma membrane. Desensitization allows the cell to manage its response to a continually large stimulus.

3.2 Adenylyl cyclase pathway

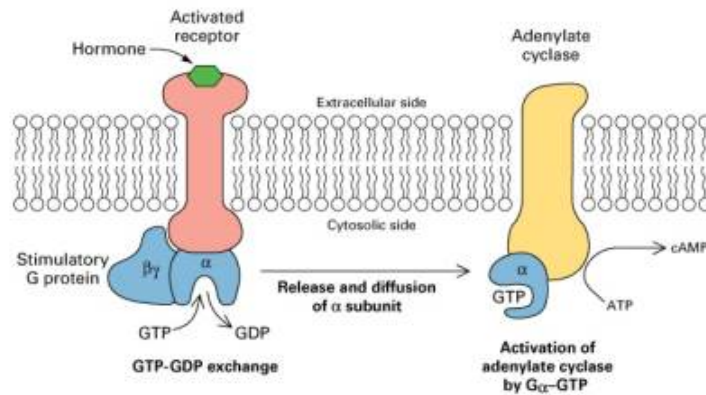


Figure 3: Adenylyl cyclase pathway *Image reproduced from Stryer, Lubert (2000) Biochemistry, 4th ed., W.H. Freeman*

Adenylyl cyclase is a plasma-membrane bound enzyme that catalyses the synthesis of cyclic AMP (cAMP) from ATP. cAMP is an important signalling molecule in the control of glycogen synthesis.

An activated α -subunit of a specific g-protein can bind to an adenylyl cyclase protein and activate it. In turn the adenylyl cyclase activates the intrinsic ATPase activity of the α -subunit causing it to hydrolyse the GTP to GDP, deactivating the subunit and the adenylyl cyclase. The α -subunit then re-associates with $\beta\gamma$. The hydrolysis of ATP is fast allowing the cell to quickly respond to changes in extra-cellular ligand concentration. When activated, the adenylyl cyclase converts ATP to cAMP. cAMP causes the activation of cyclic-AMP-dependent protein kinase (A-kinase). A-kinase catalyses the transfer of the terminal phosphate group from ATP onto receptive enzymes. The phosphorylation effects the efficacy of the enzyme for its substrate; the effect of phosphorylation on glycogenesis is described below [Alberts et al.(1994)Alberts, Bray, Lewis, Raff, Roberts, and Watson].

3.3 Phospholipase C pathway

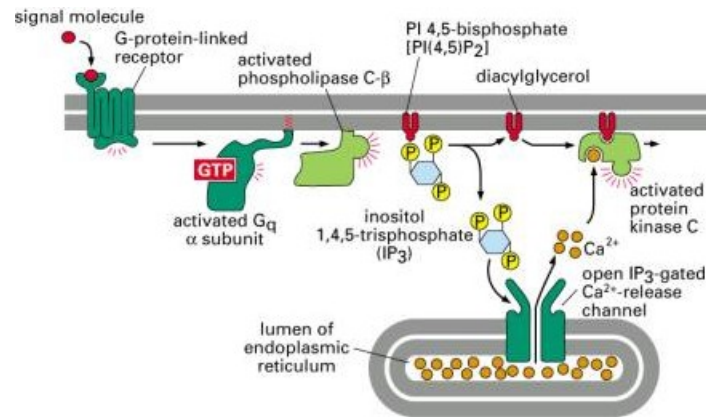


Figure 4: Phospholipase C pathway *Image reproduced from Alberts et al. Molecular Biology of the Cell, 4th Ed, Garland Publishing*

The phospholipase C pathway is responsible for the increase in cytosolic Ca^{2+} concentration due to extra-cellular stimulation. Plasma membrane and endoplasmic reticulum Ca^{2+} pumps keep the relative concentration of Ca^{2+} in the cytosol low- around $10^{-7}M$ compared to approximately $10^{-3}M$ in the extra-cellular fluid. Extra-cellular stimulation can increase the cytosolic calcium concentration tenfold.

Phospholipase C, a membrane bound enzyme, is activated by a g-protein. Phospholipase C catalyses the cleavage of phosphatidylinositol biphosphate (PIP_2 , a phospholipid thought to be located in the inner half of the plasma membrane bilayer) into inositol triphosphate (IP_3) and diacylglycerol. Both molecules are important in the signaling pathway, however only the signal induced by IP_3 is crucial to glycogenesis. IP_3 is a small water soluble molecule and can pass through the lipid bilayer and into the cytosol. In the cytosol IP_3 induces the release of Ca^{2+} from the ER by binding to IP_3 -gated Ca^{2+} -release channels in the ER membrane. The Ca^{2+} release is enhanced by positive feedback by Ca^{2+} binding to the release channels. Cytosolic Ca^{2+} effects responses in many downstream proteins.

The Ca^{2+} release is constrained in two ways; IP_3 is deactivated by rapid dephosphorylation by phosphorylases and plasma-membrane Ca^{2+} pumps remove Ca^{2+} from the cell. Some IP_3 can be phosphorylated to IP_4 which is thought to sustain slow and long calcium release [Alberts et al.(1994)Alberts, Bray, Lewis, Raff, Roberts, and Watson].

3.4 Glycogenolysis

Figure 5 depicts the control of the enzymes directly involved in the glycogenolysis. The conversion from glucose to glycogen is catalysed in the rate limiting step by glycogen synthase. Glycogen synthase has an active form (a) and an inactive form (b). Synthase phosphatase and synthase kinase respectively activate and deactivate glycogen synthase. Glycogen phosphorylase is the rate limiting enzyme for the reverse reaction from glycogen to glucose. Phosphorylase kinase and phosphatase catalyse the reactions to the active and inactive states respectively. Glucose is converted to glucose-6-phosphate for use in glycolysis. The acute regulation of hepatic glucose-6-phosphate is poorly understood, here it is assumed the concentration of glucose-6-phosphate closely follows the glucose concentration. In an intuitive sense this seems a reasonable assumption since glycogenolysis provides glucose for metabolism, and glucose must be converted to glucose-6-phosphate before it can be used in metabolism.

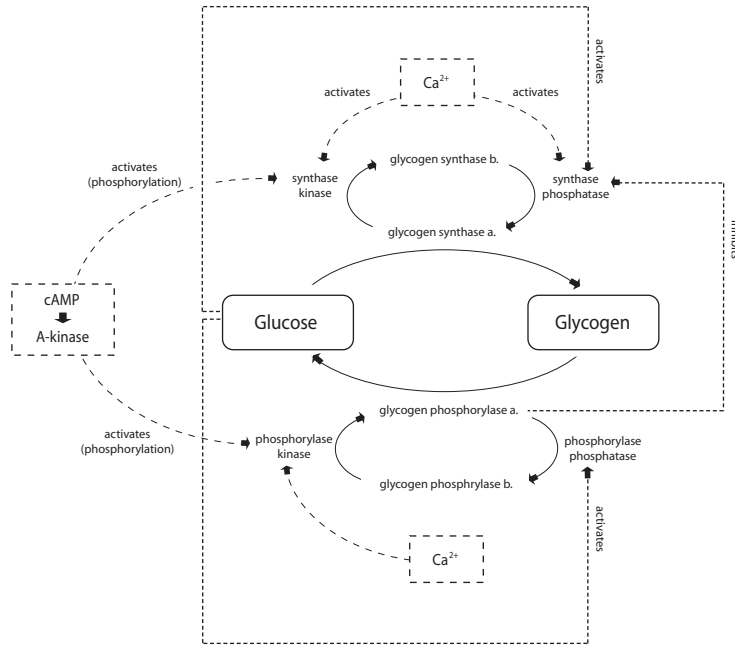


Figure 5: Control of glucose-glycogen conversion

The signalling pathways described above influence glycogenesis by selective activation or inhibition of the enzymes that control production of the active forms of glycogen synthase and phosphatase. Ca^{2+} activates both synthase kinase and phosphorylase kinase by changing their conformation, and inhibits synthase phosphatase. cAMP indirectly activates synthase kinase and phosphorylase kinase through phosphorylation by active A-kinase.

Glucose itself also has a self-regulatory effect on glycogenesis. Phosphorylase phosphatase is activated by binding glucose, due to an increased susceptibility to phosphorylation. Synthase phosphatase is activated by glucose-6-phosphate. The ability of these enzymes to bind glucose allows the hepatocyte to respond to blood glucose levels.

In fed animals the switch between glycogenesis and glycogenolysis is abrupt. The activity of glycogen phosphorylase decreases as the glucose concentration increases, but only when the proportion of active phosphorylase is less than about 10% does glycogen synthase become active. [Cardenas and Goldbeter(1996)] this suggests that glycogen phosphorylase a inhibits synthase phosphatase.

The modular representation of glycogen synthesis presented above is convenient and useful simplification. However the secondary modules are not entirely independent; for example Ca^{2+} interferes with cAMP production by inhibiting adenylyl cyclase, and cAMP can also stimulate the plasma membrane calcium pumps and cause an influx of Ca^{2+} into the cell.

The dynamics of the phospholipase C pathway reactions are better understood than the adenylyl cyclase pathway, for example there are more enzyme-kinetic parameters available. For the sake of simplicity to allow useful comparison between cellML and sbML the adenylyl cyclase pathway will be neglected in the following mathematical models.

4 Mathematical Models

4.1 G-protein coupled receptor

The following model of g-protein coupled receptors is proposed by Riccobene et al 1999 [Riccobene et al.(1999)Riccobene, Omann, and Linderman]. An initial agonist (extra-cellular ligand) concentration is specified and the model computes the coupled g-protein response.

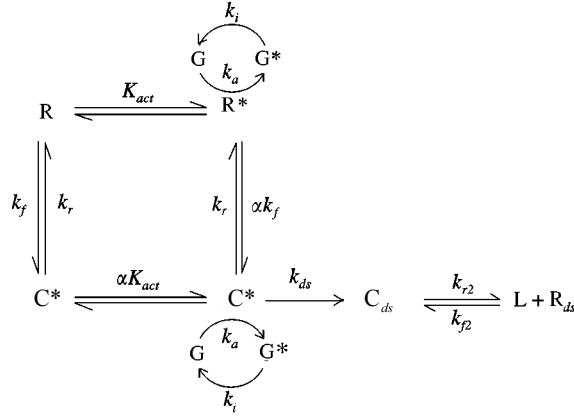


Figure 6: Riccobene et al. reaction scheme for g-protein coupled receptors

The model includes active and inactive states for the receptor that represent the different conformations of the intra-cellular side of the receptor. It is thought that types of agonists preferentially bind to a particular receptor conformation, and that the ligand-binding can effect a change in the receptor conformation at a characteristic rate. This ligand specific effect is represented by the parameter α called the ‘conformational selectivity’. The change in conformation is thought to be very fast so the reactions $R \rightleftharpoons R^*$ and $C \rightleftharpoons C^*$ are assumed to be in equilibrium.

The desensitization rate (k_{ds}) of the active ligand-receptor complex is also ligand dependent.

The receptor can only activate a g-protein when it is itself in the active state and the rate of the g-protein activation is independent of whether or not the receptor has a ligand bound. The activation of the g-protein is represented in a single reaction catalysed by the active receptor as this is thought to be rate limiting step

Applying the Law of Mass Action to the above scheme yields the following differential equations:

$$\frac{dR}{dt} = k_r C - k_f L R - k_{fR} R + \frac{k_{fR}}{K_{act} R^*} \quad (1)$$

$$\frac{dR^*}{dt} = k_r C^* - \alpha k_f L R^* + k_{fR} R - \frac{k_{fR}}{K_{act} R^*} \quad (2)$$

$$\frac{dC}{dt} = k_f L R - k_r C + \frac{k_{fR}}{\alpha K_{act} C^*} - k_{fR} C \quad (3)$$

$$\frac{dC^*}{dt} = k_{fR}C - \frac{k_{fR}}{\alpha K_{act}}C^* - k_{ds}C^* + \alpha k_f LR^* - k_r C^* \quad (4)$$

$$\frac{dC_{ds}}{dt} = k_{ds}C^* - k_{r2}C_{ds} + k_{f2}LR_{ds} \quad (5)$$

$$\frac{dR_{ds}}{dt} = k_{r2}C_{ds} - k_{f2}LR_{ds} \quad (6)$$

$$\frac{dG^*}{dt} = k_a G(C^* + R^*) - k_i G^* \quad (7)$$

$$\frac{dG}{dt} = k_i G^* - k_a G(C^* + R^*) \quad (8)$$

where:

Variable Name	Description
L	Ligand concentration
R	Receptor concentration
C	Ligand-receptor complex concentration
G	G-protein concentration

* indicates the activated form of a ligand/receptor.

The subscript $_{ds}$ indicates the desensitised form of a ligand/receptor.

Parameter	Description	Value
K_{act}	Receptor activation equilibrium constant	10^{-4}
k_{fR}	Receptor activation forward rate constant	10 s^{-1}
k_f	Complex formation rate constant	$8.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$
k_r	Complex dissociation rate constant	0.37 s^{-1}
k_{f2}	Desensitized complex formation rate constant	$8.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$
k_{r2}	Desensitized complex dissociation rate constant	$4.6 \times 10^{-3} \text{ s}^{-1}$
α	Affinity of receptor to switch between active and relaxed states	$1 \cdot 10^6$
k_a	G-protein activation rate constant	10^{-7} s^{-1}
k_i	G-protein relaxation rate constant	$2 \times 10^{-1} \text{ s}^{-1}$
k_{ds}	Receptor desensitization rate constant	$10^{-4} - 1 \text{ s}^{-1}$

4.2 Phospholipase C pathway

A simplified version of Höfer's 1999 model of calcium fluctuations is used here [Hofer(1999)]. The original model included interaction between calcium levels of neighbouring hepatic cells; these interactions are neglected here for simplicity since the markup language representations provided are for a single hepatocyte.

The model uses the IP_3 concentration to compute the cytosolic calcium concentration. Here the IP_3 concentration is taken as proportional to the active g-protein concentration with a constant decay rate. This is a simplification of the phospholipase C pathway

The model assumes spatial homogeneity inside the cytoplasm. The model computes the change in cytosolic calcium concentration by summing the relative flux of Ca^{2+} from the ER, the plasma membrane and through Ca^{2+} pumps. The model uses Li and Rinzel's model for IP_3 mediated calcium release from the ER [Li and Rinzel(1994)]. A constant background flux of Ca^{2+} into the cell across the plasma membrane is assumed and the variable flux is controlled by a first order Michaelis-Menton equation. The calcium flux out of the cytosol is governed by a second order Michaelis-Menton equation dependent on the Ca^{2+} concentration.

$$\frac{dI}{dt} = k_g G^* - k_d \quad (9)$$

$$\frac{dZ}{dt} = \rho \left[v_0 + v_c \frac{I}{K_0 + I} - v_4 \frac{Z^2}{K_4^2 + Z^2} + \alpha \left(k_r(Z, I) \frac{Z - (1 + \beta)Z}{\beta} - v_3 \frac{Z^2}{K_3^2 + Z^2} \right) \right] \quad (10)$$

$$\frac{dW}{dt} = \rho \left(v_0 + v_c \frac{I}{K_0 + I} - v_4 \frac{Z^2}{K_4^2 + Z^2} \right) \quad (11)$$

where the IP_3 release function $k_r(Z, I)$ is given by:

$$k_r(Z, I) = k_1 \frac{\left(d_2 \frac{d_1 + I}{d_3 + I} I Z \right)^3}{(d_P + I)^3 (d_a + Z)^3 \left(d_2 \frac{d_1 + I}{d_3 + I} + Z \right)^3} + k_2 \quad (12)$$

Variable Name	Description
Z	Cytosolic Ca^{2+} concentration
W	Whole cell Ca^{2+} concentration
I	IP_3 concentration

Parameter	Description	Value
k_g	rate of g-protein controlled production of IP_3	
k_d	constant IP_3 decay rate	
ρ	ratio of the total area of the plasma membrane to the effective cytosolic calcium capacity	
α	ratio of the total area of the ER to the total area of the plasma membrane	2
β	ratio of the effective calcium capacity of the ER to the effective cytosolic calcium capacity	0.1
k_1	rate constant for IP_3 mediated release of Ca^{2+} from ER	40 s^{-1}
k_2	rate constant for small leak flux of Ca^{2+} into cytosol	0.02 s^{-1}
d_a	threshold constant for Ca^{2+} mediated fast release of Ca^{2+} from ER	$0.4 \mu\text{M}$
d_p	threshold constant for IP_3 mediated fast release of Ca^{2+} from ER	$0.2 \mu\text{M}$
d_1	fit paramter for IP_3 mediated sustained Ca^{2+} from ER	$0.3 \mu\text{M}$
d_2	fit paramter for IP_3 mediated sustained Ca^{2+} from ER	$0.4 \mu\text{M}$
d_3	fit paramter for IP_3 mediated sustained Ca^{2+} from ER	$0.2 \mu\text{M}$
v_3	rate constant for Ca^{2+} uptake from cytosol into ER	$9.0 \mu\text{Ms}^{-1}$
K_3	Michaelis constant for Ca^{2+} uptake from cytosol into ER	$0.12 \mu\text{M}$
v_4	rate constant for Ca^{2+} flux out of cell across cell membrane	$3.6 \mu\text{Ms}^{-1}$
K_4	Michaelis constant for Ca^{2+} flux out of cell across cell membrane	$0.12 \mu\text{M}$
v_0	Constant rate of background Ca^{2+} flux into cell across cell membrane	$0.2 \mu\text{Ms}^{-1}$
v_c	Maximal rate for IP_3 induced Ca^{2+} flux into cell across cell membrane	$4.0 \mu\text{Ms}^{-1}$
K_0	Michaelis constant for IP_3 induced Ca^{2+} flux into cell across cell membrane	

4.3 Glucose and glycogen synthesis

A commonly used model of glucose-glycogen conversion is the minimal bicyclic cascade model of Cardenas and Goldbeter [Cardenas and Goldbeter(1996)]. The feedback from the glucose concentration regulates glycogen production. Here the slightly modified version of the Cardenas and Goldbeter model, due to Gall, Baus and Dupont [Gall et al.(2000)Gall, Baus, and Dupont], is used due to the incorporation of calcium control of glycogen phosphorylase. In the modified version, initial concentrations of Ca^{2+} , Glucose and Glucose-6-phosphate are specified and the model computes the fraction of active glycogen synthase and glycogen phosphorylase.

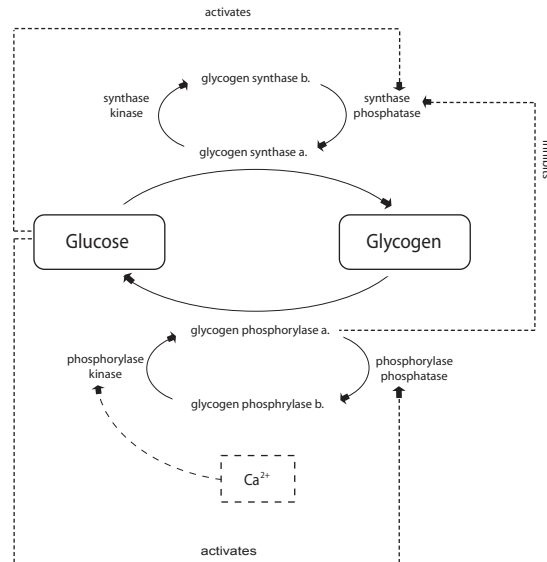


Figure 7: The Cardenas et al. model of glycogenolysis with Gall's calcium extension

In the minimal bicyclic cascade model, the only factors affecting the rate of glycogenesis that are considered are: activation of phosphorylase phosphatase by glucose, activation of synthase phosphatase by glucose-6-phosphate and the inhibition of glycogen synthase phosphatase by glycogen phosphorylase a. The model assumes a well mixed cytosol and constant cAMP concentrations which implies that the kinases work at a constant rate.

The effect of Ca_{2+} is to stimulate phosphorylase kinase by increasing the maximum rate of the enzyme (V_1) and decrease the Michaelis constant (K_1). The maximum rate equation has the form *constant + hill function* to represent the activity of phosphorylase kinase in the absence of calcium stimulation.

$$\frac{dP}{dt} = \frac{V_1(1-P)}{K_1 + 1 - P} - \frac{V_{M2} \left(1 + \frac{1+\alpha U}{K_{a1}+U}\right)}{\frac{K_2 U}{1+K_{a2}} + P} \quad (13)$$

$$\frac{dS}{dt} = \frac{V_{M3} \left(1 + \frac{\beta Y}{K_{a3}+Y} \frac{K_1}{K_1+Y}\right) (1-U)}{\frac{K_3 Y}{1+K_{a4}} + 1 - U} - \frac{V_4 U}{K_4 + U} \quad (14)$$

V_1 and K_1 are the enzyme kinetic parameters for the conversion between active and inactive forms of Glycogen phosphorylase. They have Ca^{2+} dependance:

$$V_1 = V_{M1} \left(1 + \gamma \frac{Z^4}{K_{a5}^4 + Z^4}\right) \quad (15)$$

$$K_1 = \frac{K_1^1}{1 + K_{a6}^4} \quad (16)$$

The effective change in glucose concentration can then be approximated by:

$$\frac{dU}{dt} = V_{U+}P - V_{U-}S \quad (17)$$

and similarly for the glycogen concentration¹:

$$\frac{dQ}{dt} = m(V_{U-}S - V_{U+}P) \quad (18)$$

The glucose-6-phosphate concentration is matched to the concentration of glucose with a time delay:

$$\frac{dY}{dt} = \frac{(U - Y)}{\tau} \quad (19)$$

¹Since glycogen is a polymer, the glycogen concentration can be represented by the equivalent concentration of the component glucose molecules.

This equation has the solution $Y = U + (Y_{t=0} - U) e^{-t/\tau}$. At short times the concentration of glucose-6-phosphate (Y) is approximately its initial concentration and tends towards the glucose concentration (U) with time delay τ as time increases.

where:

Variable Name	Description
S	Fraction of active glycogen synthase
P	Fraction of active glycogen phosphorylase
Z	Cytosolic Ca^{2+} concentration
U	Glucose concentration
Y	Glucose-6-phosphate concentration
Q	Effective glycogen concentration

Parameter	Description	Value
K_2	Michaelis constant for phosphorylase phosphatase activation by glucose	0.2
V_{M2}	Maximum rate of phosphorylase phosphatase activation by glucose	0.6 min^{-1}
K_{a2}	Activation constant for phosphorylase phosphatase	10mM
α	Amplification factor for rate of activated phosphorylase phosphatase by glucose	9
K_3	Michaelis constant for synthase phosphatase activation by glucose-6-phosphate	0.4
V_{M3}	Maximum rate of synthase phosphatase activation by glucose-6-phosphate	0.05 min^{-1}
K_{a4}	Activation constant for synthase phosphatase	0.5 mM
β	Amplification factor for rate of activated synthase phosphatase by glucose-6-phosphate	9
K_4	Michaelis constant for synthase phosphatase	0.4
V_4	Maximum rate of synthase phosphatase	0.2 min^{-1}
$V_{U+/-}$	Maximum rate of glycogen phosphatase and glycogen synthase respectively	
m	Mean number of molecules of glucose in a glycogen molecule	
K_{11}	Michaelis constant for activation of phosphorylase kinase by Ca^{2+}	0.1
V_{M1}	Maximum activation rate of phosphorylase kinase by Ca^{2+}	1.5 min^{-1}
K_{a5}	Further activation constant for phosphorylase kinase activation by Ca^{2+}	$0.5 \mu\text{M}$
K_{a6}	Activation constant for phosphorylase kinase Ca^{2+}	$0.5 \mu\text{M}$
γ	Factor for rate increase of phosphorylase kinase due to Ca^{2+} activation	9

The following of information between these models is depicted in figure 8.

5 A brief outline of XML

XML (extensible markup language) is a text based meta-language (a meta-language is used to describe other languages). XML is defined by the W3C and is a commonly used language for storing and exchanging data [W3C(a)]. It is written in SGML (standard generalised markup language) the international standard for defining markup languages [W3C(b)]. sbML and cellML are languages that are described by XML.

XML documents have a formal structure. Each document has a root *element* which can contain child elements; in the example below ‘letter’ is the root element and has child elements ‘to’, ‘from’, ‘message’, and ‘file’. The parent-child relationship can continue giving XML documents a nested structure. Each element can have a number of *attributes* that might, for example, uniquely identify an element. In the example below the *id* attribute identifies each of the two files being sent. Elements enclose information and hence describe the information they enclose.

The grammar of a particular XML document may be specified by an *XML schema*. The schema defines the

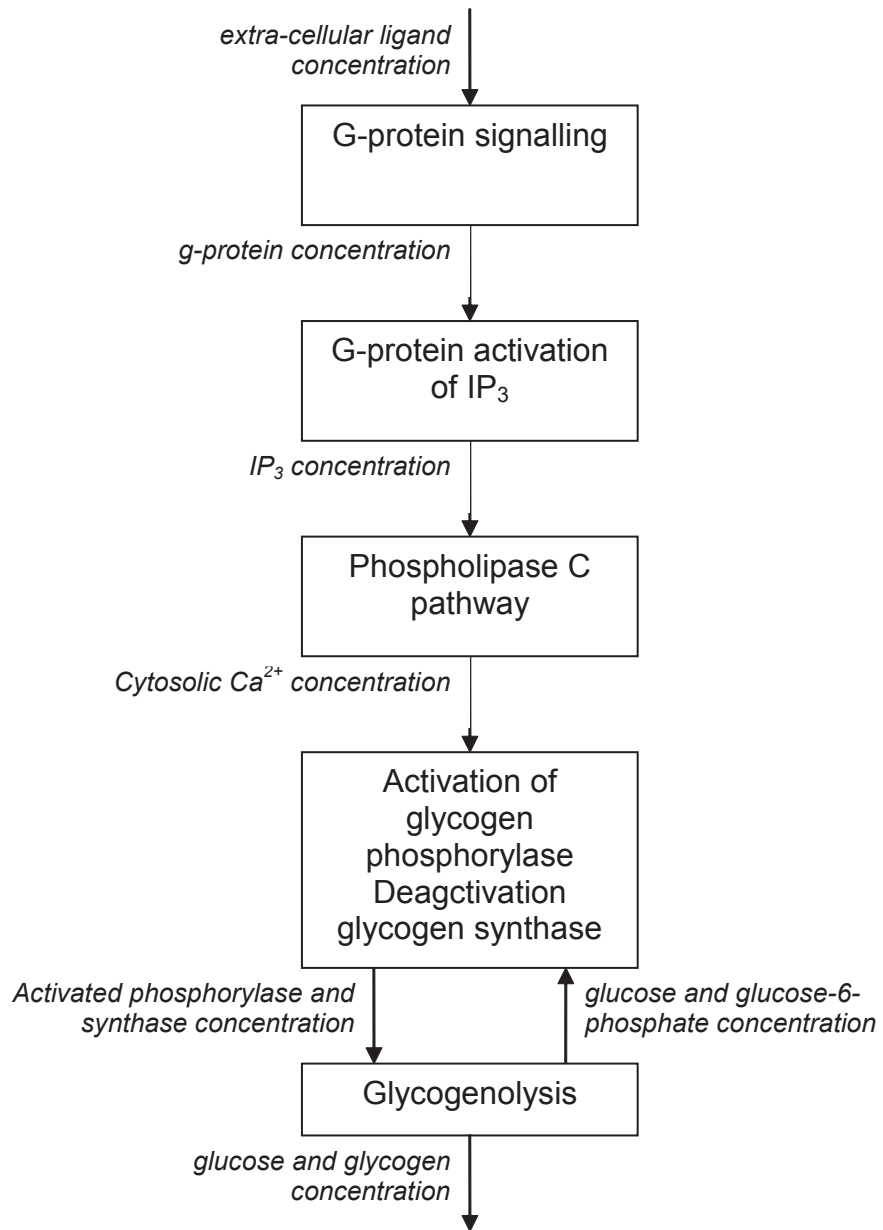


Figure 8: Information flow between modules

```

<letter>
  <to> Dr X </to>
  <from> Dr Y </to>
  <message>
    I've attached two versions of our results so you can choose the best for our paper!
  </message>
  <file id1="file1"> results1.res </file>
  <file id1="file2"> results2.res </file>
</letter>

```

Figure 9: A simple XML document

elements and their attributes that are acceptable in the XML document. Grammar may also be specified by a *DTD* (document type definition), although this is an older technology and has less control over an XML document than an XML schema. An XML document can also define a number of *namespaces*. A namespace is the collection of element names used in a particular XML document specified by a unique URI (uniform resource identifier, a unique name to identify a particular resource). For example both cellML and sbML use a subset of the mathML namespace to define mathematical equations. mathML is the W3C standard markup language for exchanging mathematical equations [W3C(d)].

6 sbML

sbML stands for ‘Systems Biology Markup Language’ and is a community led project initiated at the Californian Institute of Technology in the year 2000. Despite its rather grandiose title, sbML is a language for representing biochemical reaction networks. In essence, the language is used to define chemical entities that are linked and manipulated by reactions. The reactions can transform an entity into another entity, or move its physical location. The current version of sbML is sbML level 2, released in June 2003 [Finney and Hucka(2003)].

6.1 Language structure

The primary structure in an sbML document is a *Model*. A *Model* may contain a number of child elements; *notes*, *functions*, *units*, *compartments*, *species*, *parameters*, *rules*, *reactions* and *events*.

The *notes* section is used to describe meta-data for the model. The meta-data is typically presented in XHTML (XHTML is XML compliant HTML). Information such as the model’s author, references and the author of the cellML are provided here. This information is not compulsory.

The *functions* section defines mathematical functions that are repeatedly required by the model. For example the function $f(x) = x^2$ may be used on a number of occasions throughout the model. The functions are defined in mathML.

The *units* section defines units that are used throughout the model, for example the molar concentration of a particular species. Custom units are derived from a set of pre-defined units.

The *compartments* section defines physical bounded compartments that may contain species. The size and dimension of the compartment may be specified. The relationship between compartments is limited to

whether a particular compartment is located inside another or not. A model must contain at least one compartment as all species must reside within a compartment. Examples are a cytosol or the endoplasmic reticulum.

The *species* section defines the chemical agents in the reaction scheme. A species can be a reactant or an enzyme and can be anything from a simple ion or a complex polymer like RNA. The size, charge and initial amount of the substance can be specified, along with any boundary conditions for the substance; for example a particular species might have a constant concentration throughout the model.

The *parameters* section holds details about any global parameters in the model. Parameters may vary during a reaction; for example a rate parameter could depend on the concentration of a reactant. Parameters that are specific to a particular reaction can also be assigned in the local namespace of the reaction.

The *reactions* section describes chemical or physical transformations in the model. These can be chemical reactions, enzyme reactions or chemical transport. Reactions are defined in terms of *reactants* and *products*, with the ability to specify *modifiers* (species that contribute in some way to the reaction without being modified themselves- typically enzymes). A reaction can have an optional rate law that is expressed in mathML. The direction of the reaction is decided by the specified stoichiometry of the reactants and products.

rules are used to express transformations that cannot be expressed as *reactions*. *rules* are mathematical expressions written in mathML and can be one of essentially two types; *rate rules* to express differential equations and *algebraic rules* and *assignment rules* to express algebraic equations. *rules* are used to express a change in a property of a *species* or a change in *parameter* value. *reactions* are the preferred abstraction to express transformations and can store more information than *rules*. *reactions* have an implicit direction and the roles of chemicals in a reaction are clearly defined.

events are used to express sudden environmental changes or discontinuities in a reaction scheme. An example of a discontinuity could be that the concentration of a species X is halved when the concentration of Y exceeds a threshold. *events* are defined by a *trigger*, an optional *delay* then an *event assignment*. The *event assignment* can specify the change in a *species* quantity, a *parameter* value or a *compartment* size. *event assignments* are specified in mathML.

Elements are identified by a unique *id* attribute. The *id* attribute follows strict naming rules and allows reference between sbML entities. Rules are not permitted to have an *id* attribute - this reflects the lower status of *rules* compared to *reactions* in sbML. Elements that are allowed an *id* attribute are also allowed a *name* attribute. A *name* is a human readable description of an element.

6.2 Using sbML

See the appendix section 12.1 for the sbML code listings. The following is a personal account of the experience of coding in sbML.

I found encoding models in sbML relatively straight forward. The *parameter* and *variable* sections make managing variable and parameter definitions straightforward. Function definitions are also a convenient feature of sbML; once defined a function can be referred to in any subsequent mathML element by using standard mathML syntax for functions with the identifier element (`< ci >`) referencing the function name.

I had to choose whether to encode the modules using the *reaction* or *rule* constructs. *reactions* are primarily designed to encode chemical transformations that have clearly defined reactants (for example $A + B \rightleftharpoons C$). However, published models are often presented in the form of a set of differential equations. To encode

models presented as differential equations using the reaction construct the differential equations must first be translated back into a stoichiometric reaction scheme. Sometimes this translation was unfeasible. I used the *reaction* construct for the g-protein linked receptor module and the *rule* construct for the phospholipase C and glycogenolysis modules.

Numerous computational models exist for each module in the glycogenolysis system presented above. When examining the system as a whole it may be necessary to replace a model of a particular module with another model. sbML does not provide any encapsulation methods; all variables and global parameters are accessible throughout the sbML document. To ensure the necessary autonomy of individual models I found it necessary to encode each module in a separate sbML document. Furthermore sbML does not currently provide any import facilities. Therefore, a third-party sbML interpreter would be required to link each separately encoded module in the glycogenolysis system. Lack of import facilities also means that re-using sbML code is difficult. The next version of sbML (level 3) hopes to address this issue.

I validated my sbML code using the online sbML validation tool [sbML(2)]. I was also able to visualise the models using this tool (for the result of this visualisation see the appendix section 12.3). There is no DTD or XML schema available for sbML.

sbML level 2 uses the same meta-data scheme as cellML (cellML uses the rdf framework described below). However this is poorly documented in the sbML specification, and none of the examples I examined used the rdf framework for their meta-data, presenting metadata in XHTML in the initial notes section.

7 cellML

cellML is developed at the Bioengineering Institute at the University of Auckland, New Zealand. Development is led by a research team at the university and reviewed by an international advisory board. cellML is a language for describing any process at the cellular level such as electrophysical, chemical, physical processes. This generality necessitates that cellML is more abstract than sbML. The current accepted specification of cellML is version 1.0 released in August 2001, although a draft version of the 1.1 specification has been available since September 2003 [cellML()]. I used cellML 1.1 in this essay.

7.1 Language structure

The root element in cellML is a *model*. A *model* encapsulates *import*, *unit*, *component*, *group* and *connection* elements.

The *units* section defines units used throughout the model and is very similar to the *units* section in sbML.

A *component* is the smallest functional unit in cellML. For example a component could represent a particular pathway, a physical intra-cellular entity like a mitochondria or a reaction. Each *component* encloses *units*, *variables* and an optional *reaction* and numerous *math* elements. *components* are primarily defined in terms of the *variables* they modify. *variables* can represent physical species such as reactants, or be the value of a parameter. A *variable* is identified by a name unique to its parent component, has a specified *public_interface* and *private_interface* that determines whether the variable is accessible by sibling or encapsulated components respectively. A *variables* may also have a stoichiometry. Variables can be modified in *math* elements where mathML is used to specify the equations that alter the value of a variable.

The optional *reaction* element is designed to represent chemical reactions. *reactions* can be one of three

types; mathematical equations, quantitative chemical expressions (when the reaction can be expressed mathematically) or qualitative chemical expressions (a simple chemical pathway diagram without stoichiometries and rates). Essentially, the *reaction* element encloses a number of *variable_ref* elements that refer to variables defined in the parent *component*. Each referenced variable has a defined *role*, that could be a *reactant* or *product* for qualitative reactions or specified by a *math* element.

The *group* element describes logical and physical relationships between components. There are two types of predefined relationships; *containment* and *encapsulation*. *containment* describes physical relationships between components; for example a cell would contain a cytosol. *encapsulation* defines a logical hierarchy between components, where the encapsulating component hides the details of the child. The result is a ‘black box’ or sub-model. Any variables in the child components must be referenced through the parent component. It is possible to define new relationships although these will not be understood generic cellML interpreters.

connection elements are used to link variables between different components. A *connection* element references two components and the encapsulated variables that should be linked. The *interface* attributes of a variable (defined in the component) determine which component receives the value of the linked variable.

The *import* element was introduced in cellML 1.1 and is used to import *components* and *units* from other models. This allows cellML descriptions to be reused. The imported components and units behave in the same way components and units defined in the current model. The W3C hyperlink standard Xlink is used to refer to other models [W3C(2001)] .

cellML has formal support for meta-data. cellML utilises the rdf (resource description framework) [W3C(c)] and a number of widely-used meta-data description namespaces, namely: Dublin Core [Dublin Core()], vCard [W3C and Iannella(2001)], BQS (bibliographic query service) [BQS()] which describe document properties, contact information and reference material respectively. Meta-data elements are identified with the `<rdf:RDF>` tag and can be used to describe any element of a cellML document.

7.2 Using cellML

See the appendix section 12.2 for the cellML code listings.

The *math* element rather than the *reaction* element was chosen to encode the models. This was for two reasons. Firstly I found it unclear how to manage parameters when using the *reaction* element of a *component*. Each referenced variable in a *reaction* requires a defined *role* and I could not find a suitable *role* to assign to a parameter value. Secondly cellML ‘best practice’ is to define a single *reaction* element for each *component* to ensure maximum reusability of *components* [cellML()]. Each *reaction* may contain only one *rate* equation. These restrictions mean that a *component* that encloses a *reaction* can only encode a single chemical transformation, limiting the generality of the *component*. The restriction could be overcome by using the encapsulation methods in the *group* structure, however this would imply a hierarchy in chemical reactions that might not be biologically realistic.

cellML’s support for encapsulation meant I could encode the entire model of the glycogenolysis system in a single cellML document without jeopardising the autonomy of individual modules. Rather than the using the explicit encapsulation in the *group* element, I found the implicit encapsulation provided by a *component* was sufficient to encode the model. Linking the *components* is very easy when using the *connection* element.

The validation tools available for cellML are poor compared to sbML. There are no online validation tools or automatic visualisation tools. A validation program is available for download on the cellML website, however

the program will only run on Redhat Linux, and comes with no documentation or source code. Sparse comments on the cellML website note that the validator has poor support for mathML, and consequently I was unable to validate my code using the software. A cellML DTD is provided on the cellML website, however DTD's do not support multiple namespaces and there is currently no DTD available for rtf documents so the cellML DTD is an insufficient way to validate a cellML document.

The support for meta-data in cellML is excellent and there are many examples of well annotated cellML models on the cellML website.

8 Comments

The Beacon Project team envisage the existence of an online 'parameter database' that provides the currently accepted 'best' parameter values as required. At present support for such a database would be impossible in sbML due to the lack of an import method. cellML could support the parameter database but only if it provided parameters as part of a *component*. However, for both languages external database support could be provided by the interpreter.

Neither cellML nor sbML has formal meta-data support for representing the assumptions a model is based on. Evaluating the assumptions in a model is crucial to selecting a suitable model for a particular component of a system. Having meta-data about assumptions would allow a catalogue of models to be searched by a model's assumptions; modularity of models would then allow a particular model to be inserted and assessed in the context of the entire system.

Support for the validation of a model against experimental data (or verified simulation data) is not present in either language.

The support for mathML in both sbML and cellML is sensible. Although writing mathML by hand is laborious, it is a well supported standard and can be automatically generated by many programs such as MAPLE. sbML Level 1 did not support mathML so many current examples of sbML contain the sbML specific mathematical language.

sbML is well supported by third-party software. Third-party software support for cellML is much more sparse. The availability of software support is an important consideration when choosing an exchange format since the exchange format has no value unless it can be interpreted. The cellML and sbML teams are working to ensure interoperability between the two languages by developing tools to convert chemical pathway models.

Systems Biology requires integration of models across different length scales. cellML is being developed in conjunction with other languages: in the future cellML will integrate with AnatML to provide an exchange format for models of whole organs.

Currently support for spatial features is limited in both languages; sbML defines spatial characteristics through the *compartment* construct, and relationships between compartments are limited to the containment of one compartment by another. cellML defines spatial characteristics through its grouping construct which also only allows containment. Both languages are restricted by their current lack of support for spatially varying variables.

Support for mathematical constructs is also limited in both languages. For example neither language supports difference equations.

9 Conclusion

sbML and cellML are both fledgling technologies. At present sbML is too specific to biochemical network models to be able to efficiently model the wide range of intra-cellular processes. The lack of encapsulation and import support is a major handicap for sbML, but this will be addressed in a future release. cellML is more abstract and hence able to model a wider range of cellular phenomenon than sbML. Coupling cellML's generality with its close ties to AnatML makes cellML more attractive than sbML for cellular process modelling. However, better integration with external data sources, the ability to be able to precisely handle spatial characteristics and support for a wider range of mathematical constructs is needed before cellML is an appropriate technology for Systems Biology.

10 Acknowledgements

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11 References

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12 Appendix

12.1 sbML code

12.1.1 G-protein linked receptor

The following code is available electronically at:

http://www.homepages.ucl.ac.uk/~ucbptag/essay1/xml/sbML_glycogenolysis_gprotein.xml

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model id="Gprotein_linked_receptor">
    <notes>
      <body xmlns="http://www.w3.org/1999/xhtml">
        <p>
          G-protein linked receptor model of Riccobene et al. 1999
        </p>
      </body>
    </notes>
    <listOfCompartments>
      <compartment id="cell" size="1"></compartment>
    </listOfCompartments>
    <listOfSpecies>
```

```

    <species boundaryCondition="true" compartment="cell" constant="true" id="L" name="extracellular
ligand"></species>
    <species compartment="cell" id="R" name="relaxed receptor"></species>
    <species compartment="cell" id="Ra" name="activated receptor"></species>
    <species compartment="cell" id="Rds" name="activated receptor"></species>
    <species compartment="cell" id="C" name="relaxed receptor-ligand complex"></species>
    <species compartment="cell" id="Ca" name="activated receptor-ligand complex"></species>
    <species compartment="cell" id="Cds" name="desensitized receptor-ligand complex"></species>
    <species compartment="cell" id="G" name="relaxed G-protein"></species>
    <species compartment="cell" id="Ga" name="activtaed G-protein"></species>
</listOfSpecies>
<listOfParameters>
    <parameter id="Kact" name="receptor activation equilibrium constant"></parameter>
    <parameter id="kfR" name="receptor activation forward rate constant"></parameter>
    <parameter id="kf" name="complex formation rate constant"></parameter>
    <parameter id="kr" name="complex dissociation rate constant"></parameter>
    <parameter id="kf2" name="desensitized complex formation rate constant"></parameter>
    <parameter id="kr2" name="desensitized complex dissociation rate constant"></parameter>
    <parameter id="alpha" name="affinity of receptor to switch between active and relaxed sites"></
parameter>
    <parameter id="ka" name="g-protein activation rate constant"></parameter>
    <parameter id="ki" name="g-protein relaxation rate constant"></parameter>
    <parameter id="kds" name="g-protein desensitization rate constant"></parameter>
</listOfParameters>
<listOfReactions>
    <reaction fast="true" id="R_act" name="unbound receptor activation">
    <listOfReactants>
        <speciesReference species="R" stoichiometry="1"></speciesReference>
    </listOfReactants>
    <listOfProducts>
        <speciesReference species="Ra" stoichiometry="1"></speciesReference>
    </listOfProducts>
    <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
    <plus></plus>
    <apply>
    <minus></minus>
    <apply>
    <times></times>
    <ci>
    kf
    </ci>
    <ci>
    R
    </ci>
    </apply>
    </apply>
    </apply>
    <apply>
    <divide></divide>
    <ci>
    kfR
    </ci>
    <apply>
    <times></times>
    <ci>
    Kact
    </ci>
    <ci>

```

```

    Ra
  </ci>
</apply>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R_bind" name="relaxed receptor ligand binding">
  <listOfReactants>
    <speciesReference species="R" stoichiometry="1"></speciesReference>
    <speciesReference species="L" stoichiometry="1"></speciesReference>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="C" stoichiometry="1"></speciesReference>
  </listOfProducts>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply id="id8">
        <minus></minus>
        <apply>
          <times></times>
          <ci>
            kr
          </ci>
          <ci>
            C
          </ci>
        </apply>
        <apply>
          <times></times>
          <ci>
            kf
          </ci>
          <ci>
            L
          </ci>
          <ci>
            R
          </ci>
        </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
<reaction id="Ra_bind" name="activated receptor ligand binding">
  <listOfReactants>
    <speciesReference species="Ra" stoichiometry="1"></speciesReference>
    <speciesReference species="L" stoichiometry="1"></speciesReference>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="Ca" stoichiometry="1"></speciesReference>
  </listOfProducts>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus></minus>
        <apply>
          <times></times>

```



```

    <ci>
      kr
    </ci>
    <ci>
      Ca
    </ci>
  </apply>
</apply>
<times></times>
  <ci>
    kf
  </ci>
  <ci>
    L
  </ci>
  <ci>
    Ra
  </ci>
  <ci>
    alpha
  </ci>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction fast="true" id="C_act" name="bound receptor activation">
  <listOfReactants>
    <speciesReference species="C" stoichiometry="1"></speciesReference>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="Ca" stoichiometry="1"></speciesReference>
  </listOfProducts>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
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        <apply>
          <times></times>
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            kfR
          </ci>
          <ci>
            C
          </ci>
        </apply>
      </apply>
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      <ci>
        kfR
      </ci>
      <apply>
        <times></times>
        <ci>
          alpha
        </ci>
        <ci>
          Kact
        </ci>
      </apply>
    </math>
  </kineticLaw>
</reaction>

```

```

        <ci>
          Ca
        </ci>
      </apply>
    </apply>
  </math>
</kineticLaw>
</reaction>
<reaction id="G_act" name="G-protein activation">
  <listOfReactants>
    <speciesReference species="G" stoichiometry="1"></speciesReference>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="Ga" stoichiometry="1"></speciesReference>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="Ra"></modifierSpeciesReference>
    <modifierSpeciesReference species="Ca"></modifierSpeciesReference>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus></minus>
        <apply>
          <times></times>
          <ci>
            ka
          </ci>
          <ci>
            G
          </ci>
          <apply>
            <plus></plus>
            <ci>
              Ca
            </ci>
            <ci>
              Ra
            </ci>
          </apply>
        </apply>
      </times></times>
      <ci>
        ki
      </ci>
      <ci>
        Ga
      </ci>
    </apply>
  </math>
</kineticLaw>
</reaction>
<reaction id="Ca_ds" name="Complex desensitization">
  <listOfReactants>
    <speciesReference species="Ca" stoichiometry="1"></speciesReference>
  </listOfReactants>

```

```

<listOfProducts>
  <speciesReference species="Cds" stoichiometry="1"></speciesReference>
</listOfProducts>
<kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times></times>
      <ci>
        kds
      </ci>
      <ci>
        Ca
      </ci>
    </apply>
  </math>
</kineticLaw>
</reaction>
<reaction id="Cds_bind" name="C Desenitized complex bind">
  <listOfReactants>
    <speciesReference species="Cads" stoichiometry="1"></speciesReference>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="L" stoichiometry="1"></speciesReference>
    <speciesReference species="Rds" stoichiometry="1"></speciesReference>
  </listOfProducts>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
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        <apply>
          <times></times>
          <ci>
            kr2
          </ci>
          <ci>
            Cds
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        <apply>
          <times></times>
          <ci>
            kf2
          </ci>
          <ci>
            L
          </ci>
          <ci>
            Rds
          </ci>
        </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
</listOfReactions>
</model>
</sbml>

```

12.1.2 Phospholipase C pathway

The following code is available electronically at:

http://www.homepages.ucl.ac.uk/~ucbptag/essay1/xml/sbML_glycogenolysis_phospholipaseC.xml

```
<?xml version="1.0" encoding="UTF-8"?>
  <sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
    <model id="Phospholipase_C_pathway" name="A simplified version of Hofer's 1999 model of IP3 induced calcium release">
      <notes>
        <body xmlns="http://www.w3.org/1999/xhtml">
          <p>
            Phospholipase C pathway.
          </p>
          <p>
            A simplified version of Hofer's 1999 model of calcium fluctuations.
          </p>
        </body>
      </notes>
      <listOfFunctionDefinitions>
        <functionDefinition id="fn_kr" name="kr(Z,I)">
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <bvar>
              <ci>
                Z
              </ci>
              <ci>
                I
              </ci>
            </bvar>
            <apply>
              <plus></plus>
              <apply>
                <divide></divide>
                <apply>
                  <times></times>
                  <ci>
                    k1
                  </ci>
                  <apply>
                    <power></power>
                    <ci>
                      d2
                    </ci>
                    <cn>
                      3
                    </cn>
                  </apply>
                </apply>
              </apply>
              <power></power>
              <apply>
                <plus></plus>
                <ci>
                  d1
                </ci>
                <ci>
                  I
                </ci>
              </apply>
            </math>
          </functionDefinition>
      </listOfFunctionDefinitions>
    </model>
  </sbml>

```

```

    </ci>
  </apply>
  <cn>
    3
  </cn>
</apply>
<apply>
  <power></power>
  <ci>
    I
  </ci>
  <cn>
    3
  </cn>
</apply>
<apply>
  <power></power>
  <ci>
    Z
  </ci>
  <cn>
    3
  </cn>
</apply>
</apply>
<apply>
  <times></times>
  <apply>
    <power></power>
    <apply>
      <plus></plus>
      <ci>
        d3
      </ci>
      <imaginaryi></imaginaryi>
    </apply>
    <cn>
      3
    </cn>
  </apply>
  <apply>
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      <plus></plus>
      <ci>
        dP
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      <ci>
        I
      </ci>
    </apply>
    <cn>
      3
    </cn>
  </apply>
<apply>
  <power></power>
  <apply>
    <plus></plus>

```

```

    <ci>
      da
    </ci>
    <ci>
      Z
    </ci>
  </apply>
  <cn>
    3
  </cn>
</apply>
<apply>
  <power></power>
  <apply>
    <plus></plus>
  <apply>
    <divide></divide>
  <apply>
    <times></times>
    <ci>
      d2
    </ci>
  <apply>
    <plus></plus>
    <ci>
      d1
    </ci>
    <ci>
      I
    </ci>
  </apply>
</apply>
<apply>
  <plus></plus>
  <ci>
    d3
  </ci>
  <ci>
    I
  </ci>
</apply>
</apply>
<ci>
  Z
</ci>
</apply>
<cn>
  3
</cn>
</apply>
</apply>
</apply>
<ci>
  k2
</ci>
</apply>
</math>
</functionDefinition>
</listOfFunctionDefinitions>

```

```

<listOfCompartments>
  <compartment id="wholecell" size="1"></compartment>
  <compartment id="cytosol" outside="wholecell" size="1"></compartment>
</listOfCompartments>
<listOfSpecies>
  <species compartment="cytosol" id="Z" name="cytosolic Ca2+ concentration"></species>
  <species compartment="wholecell" id="W" name="Whole cell Ca2+ concentration"></species>
  <species compartment="cytosol" id="I" name="IP3 concentration"></species>
</listOfSpecies>
<listOfParameters>
  <parameter id="rho" name="ratio area of plasma membrame to effective cytosolic calcium capacity
"></parameter>
  <parameter id="alpha" name="ratio of area of ER to area of plasma membrame"></parameter>
  <parameter id="beta" name="ratio of effective calcium capacity of ER to effective cytosolic cal
cium capacity"></parameter>
  <parameter id="k1" name="IP3 mediated release of Ca2+ from ER rate constant"></parameter>
  <parameter id="k2" name="small leak flux of Ca2+ into cytosol rate constant"></parameter>
  <parameter id="da"></parameter>
  <parameter id="dp"></parameter>
  <parameter id="d1"></parameter>
  <parameter id="d2"></parameter>
  <parameter id="d3"></parameter>
  <parameter id="v3" name="Ca2+ uptake from cytosol into ER rate constant"></parameter>
  <parameter id="K3" name="Michaelis constant for Ca2+ uptake from cytosol into ER"></parameter>

  <parameter id="v4" name="Ca2+ flux out of cell across cell membrane rate constant"></parameter>

  <parameter id="K4" name="Michaelis constant for Ca2+ flux out of cell across cell membrane"></p
arameter>
  <parameter id="vc" name="Maximal rate for IP3 induced Ca2+ flux into cell across cell membrane"
></parameter>
  <parameter id="K0" name="Michaelis constant for IP3 induced Ca2+ flux into cell across cell mem
brane"></parameter>
</listOfParameters>
<listOfRules>
<rateRule variable="Z">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times></times>
      <ci>
        rho
      </ci>
      <apply>
        <plus></plus>
        <ci>
          v0
        </ci>
      </apply>
      <divide></divide>
      <apply>
        <times></times>
        <ci>
          vc
        </ci>
        <ci>
          I
        </ci>
      </apply>
    </apply>
  </math>

```

```

<plus></plus>
<ci>
  K0
</ci>
<ci>
  I
</ci>
</apply>
</apply>
<apply>
  <minus></minus>
  <apply>
    <divide></divide>
    <apply>
      <times></times>
      <ci>
        v4
      </ci>
    </apply>
    <power></power>
    <ci>
      Z
    </ci>
    <cn>
      2
    </cn>
  </apply>
</apply>
<apply>
  <plus></plus>
  <apply>
    <power></power>
    <ci>
      K4
    </ci>
    <cn>
      2
    </cn>
  </apply>
</apply>
<apply>
  <power></power>
  <ci>
    Z
  </ci>
  <cn>
    2
  </cn>
</apply>
</apply>
</apply>
<apply>
  <times></times>
  <ci>
    alpha
  </ci>
  <apply>
    <minus></minus>
  </apply>

```



```

    <apply>
      <power></power>
      <ci>
        K3
      </ci>
      <cn>
        2
      </cn>
    </apply>
  </apply>
  <apply>
    <power></power>
    <ci>
      Z
    </ci>
    <cn>
      2
    </cn>
  </apply>
</apply>
</apply>
</apply>
</apply>
</math>
</rateRule>
<rateRule variable="W">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times></times>
      <ci>
        rho
      </ci>
      <apply>
        <plus></plus>
        <ci>
          v0
        </ci>
        <apply>
          <divide></divide>
          <apply>
            <times></times>
            <ci>
              vc
            </ci>
            <ci>
              I
            </ci>
          </apply>
        </apply>
        <plus></plus>
        <ci>
          K0
        </ci>
        <ci>
          I
        </ci>
      </apply>
    </apply>
  </math>

```

```

<apply>
  <minus></minus>
  <apply>
    <divide></divide>
    <apply>
      <times></times>
      <ci>
        v4
      </ci>
      <apply>
        <power></power>
        <ci>
          Z
        </ci>
        <cn>
          2
        </cn>
      </apply>
    </apply>
  </apply>
  <apply>
    <plus></plus>
    <apply>
      <power></power>
      <ci>
        K4
      </ci>
      <cn>
        2
      </cn>
    </apply>
    <apply>
      <power></power>
      <ci>
        Z
      </ci>
      <cn>
        2
      </cn>
    </apply>
  </apply>
</math>
</rateRule>
</listOfRules>
</model>
</sbml>

```

12.1.3 Glycogenolysis

The following code is available electronically at:

http://www.homepages.ucl.ac.uk/~ucbptag/essay1/xml/sbML_glycogenolysis_glycogen.xml

```
<?xml version="1.0" encoding="UTF-8"?>
```

```

<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model id="Glycogen_synthesis" name="Glycogen Synthesis Cardenas with Gall's models">
    <notes>
      <body xmlns="http://www.w3.org/1999/xhtml">
        <p>
          Glucose - glycogen conversion model of Cardenas and Goldbeter 1996
        </p>
        <p>
          including Gall Baus and Dupont 2000 regulation by Ca2+
        </p>
        <p>
          The change in the relative glucose/glycogen concentration is computed from the difference between the activated synthase and phosphatase
        </p>
      </body>
    </notes>
    <listOfCompartments>
      <compartment id="cytosol" size="1"></compartment>
    </listOfCompartments>
    <listOfSpecies>
      <species id="S" name="fraction of active glycogen synthase"></species>
      <species id="P" name="fraction of active glycogen phosphorylase"></species>
      <species id="Z" name="cytosolic Ca2+ concentration"></species>
      <species id="U" name="Glucose concentration"></species>
      <species id="Y" name="Glucose-6-phosphate concentration"></species>
      <species id="Q" name="effective glycogen concentration"></species>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="K2" name="Michaelis constant for phosphorylase phosphatase activation by glucose"></parameter>
      <parameter id="VM2" name="Maximum rate of phosphorylase phosphatase activation by glucose"></parameter>
      <parameter id="Ka1" name="Activation constant for further activation phosphorylase phosphatase by glucose"></parameter>
      <parameter id="Ka2" name="Activation constant for phosphorylase phosphatase"></parameter>
      <parameter id="alpha" name="Amplification factor for rate of activated phosphorylase phosphatase by glucose"></parameter>
      <parameter id="K3" name="Michaelis constant for synthase phosphatase activation by glucose-6-phosphate"></parameter>
      <parameter id="VM3" name="Maximum rate of synthase phosphatase activation by glucose-6-phosphate"></parameter>
      <parameter id="Ka4" name="Activation constant for synthase phosphatase"></parameter>
      <parameter id="beta" name="Amplification factor for rate of activated synthase phosphatase by glucose-6-phosphate"></parameter>
      <parameter id="K4" name="Michaelis constant for synthase phosphatase"></parameter>
      <parameter id="V4" name="Maximum rate of synthase phosphatase"></parameter>
      <parameter id="VUf" name="Maximum rate of glycogen phosphorylase"></parameter>
      <parameter id="VUb" name="Maximum rate of glycogen synthase"></parameter>
      <parameter id="K11" name="Michaelis constant for activation of phosphorylase kinase by Ca2+"></parameter>
      <parameter id="VM1" name="Maximum activation rate of phosphorylase kinase by Ca2+"></parameter>
      <parameter id="Ka5" name="Further activation constant for phosphorylase kinase activation by Ca2+"></parameter>
      <parameter id="Ka6" name="Activation constant for phosphorylase kinase Ca2+"></parameter>
      <parameter id="gamma" name="Factor for rate increase of phosphorylase kinase due to Ca2+ activation"></parameter>
      <parameter constant="false" id="V1" name="Maximum rate for conversion between active and inactive glycogen phosphorylase"></parameter>
    </listOfParameters>
  </model>

```

```

    <parameter constant="false" id="K1" name="Michaelis parameter for conversion between active and
inactive glycogen phosphorylase"></parameter>
    <parameter id="m" name="Number of molecules of glucose in a glycogen molecule"></parameter>
    <parameter id="tau" name="Time lag for glucose-6-phosphate concentration"></parameter>
</listOfParameters>
<listOfRules>
<assignmentRule variable="V1">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
            <times></times>
            <ci>
                VM1
            </ci>
            <apply>
                <plus></plus>
                <cn>
                    1
                </cn>
                <apply>
                    <divide></divide>
                    <apply>
                        <times></times>
                        <eulergamma></eulergamma>
                        <apply>
                            <power></power>
                            <ci>
                                Z
                            </ci>
                            <cn>
                                4
                            </cn>
                        </apply>
                    </apply>
                    <plus></plus>
                    <apply>
                        <power></power>
                        <ci>
                            Ka5
                        </ci>
                        <cn>
                            4
                        </cn>
                    </apply>
                </apply>
                <power></power>
                <ci>
                    Z
                </ci>
                <cn>
                    4
                </cn>
            </apply>
        </apply>
    </math>
</assignmentRule>

```

```

<assignmentRule variable="K1">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <divide></divide>
      <ci>
        K11
      </ci>
      <apply>
        <plus></plus>
        <cn>
          1
        </cn>
        <apply>
          <power></power>
          <ci>
            Ka6
          </ci>
          <cn>
            4
          </cn>
        </apply>
      </apply>
    </math>
  </assignmentRule>
  <rateRule variable="Y">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <divide></divide>
        <apply>
          <minus></minus>
          <ci>
            U
          </ci>
          <ci>
            Y
          </ci>
        </apply>
        <ci>
          tau
        </ci>
      </apply>
    </math>
  </rateRule>
  <rateRule variable="P">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus></minus>
        <apply>
          <divide></divide>
          <apply>
            <times></times>
            <ci>
              V1
            </ci>
          </apply>
          <minus></minus>
          <cn>
            1
          </cn>
        </apply>
      </math>
    </rateRule>
  </rateRule>

```

```

    </cn>
    <ci>
    P
    </ci>
  </apply>
</apply>
<apply>
  <plus></plus>
  <ci>
    K1
  </ci>
  <cn>
    1
  </cn>
  <apply>
    <minus></minus>
    <ci>
      P
    </ci>
  </apply>
</apply>
</apply>
<apply>
  <divide></divide>
  <apply>
    <ci>
      VM2
    </ci>
  <apply>
    <plus></plus>
    <cn>
      1
    </cn>
  <apply>
    <divide></divide>
    <apply>
      <plus></plus>
      <cn>
        1
      </cn>
    <apply>
      <times></times>
      <ci>
        alpha
      </ci>
      <ci>
        U
      </ci>
    </apply>
  </apply>
</apply>
<apply>
  <plus></plus>
  <ci>
    Ka1
  </ci>
  <ci>
    U
  </ci>
</apply>

```

```

    </apply>
  </apply>
</apply>
<apply>
  <plus></plus>
  <apply>
    <divide></divide>
    <ci>
      K2
    </ci>
    <apply>
      <plus></plus>
      <cn>
        1
      </cn>
    <apply>
      <divide></divide>
      <ci>
        U
      </ci>
      <ci>
        Ka2
      </ci>
    </apply>
  </apply>
</apply>
<ci>
  P
</ci>
</apply>
</apply>
</math>
</rateRule>
<rateRule variable="S">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus></minus>
      <apply>
        <divide></divide>
        <apply>
          <times></times>
          <ci>
            VM3
          </ci>
          <apply>
            <plus></plus>
            <cn>
              1
            </cn>
          <apply>
            <divide></divide>
            <apply>
              <times></times>
              <ci>
                beta
              </ci>
            <ci>
              Y

```



```

</ci>
<ci>
  K1
</ci>
<apply>
  <minus></minus>
  <cn>
    1
  </cn>
  <ci>
    U
  </ci>
</apply>
</apply>
<apply>
  <times></times>
  <apply>
    <plus></plus>
    <ci>
      Ka3
    </ci>
    <ci>
      Y
    </ci>
  </apply>
</apply>
<apply>
  <plus></plus>
  <ci>
    K1
  </ci>
  <ci>
    Y
  </ci>
</apply>
</apply>
</apply>
</apply>
<apply>
  <plus></plus>
  <apply>
    <divide></divide>
    <ci>
      K3
    </ci>
    <apply>
      <plus></plus>
      <cn>
        1
      </cn>
    </apply>
  </divide></divide>
  <ci>
    Y
  </ci>
  <ci>
    Ka4
  </ci>
</apply>

```

```

    </apply>
  </apply>
  <cn>
    1
  </cn>
  <apply>
    <minus></minus>
    <ci>
      U
    </ci>
  </apply>
</apply>
</apply>
<apply>
  <divide></divide>
  <apply>
    <times></times>
    <ci>
      V4
    </ci>
    <ci>
      U
    </ci>
  </apply>
  <apply>
    <plus></plus>
    <ci>
      K4
    </ci>
    <ci>
      U
    </ci>
  </apply>
</apply>
</apply>
</math>
</rateRule>
</listOfRules>
<listOfReactions>
  <reaction id="dU" name="Glucose glycogen concentration">
    <listOfReactants>
      <speciesReference species="U" stoichiometry="1"></speciesReference>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="Q" stoichiometry="1"></speciesReference>
    </listOfProducts>
    <listOfModifiers>
      <modifierSpeciesReference species="P"></modifierSpeciesReference>
      <modifierSpeciesReference species="S"></modifierSpeciesReference>
    </listOfModifiers>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          <plus></plus>
          <apply>
            <minus></minus>
            <apply>
              <times></times>
              <ci>

```

```

        VUf
      </ci>
    </ci>
    p
  </ci>
</apply>
</apply>
<apply>
  <times></times>
  <ci>
    Vub
  </ci>
  <ci>
    S
  </ci>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
</listOfReactions>
</model>
</sbml>

```

12.2 cellML code

The following code is available electronically at:

http://www.homepages.ucl.ac.uk/~ucbptag/essay1/xml/cellML_glycogenolysis.xml

```

<?xml version="1.0" encoding="UTF-8"?>
  <model cmeta:id="Gprotein_controlled_glycogen_production" name="Three_moduli_model_of_glycogen_pro
duction" xmlns:cellml="http://www.cellml.org/cellml/1.0#" xmlns:cmeta="http://www.cellml.org/metadat
a/1.0#" xmlns:mathml="http://www.w3.org/1998/Math/MathML" xmlns="http://www.cellml.org/cellml/1.0#">

    <!-- Model description -->
    <rdf:RDF xmlns:bqs="http://www.cellml.org/bqs/1.0#" xmlns:dc="http://purl.org/dc/elements/1.1/" x
mlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xml
ns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#">
      <!-- cellML authoring information -->
      <rdf:Description rdf:about="">
        <!-- Created by -->
        <dc:creator rdf:parseType="Resource">
          <vCard:N rdf:parseType="Resource">
            <vCard:Family>
              Graham
            </vCard:Family>
            <vCard:Given>
              Trevor
            </vCard:Given>
            <vCard:Other>
              A
            </vCard:Other>
          </vCard:N>
          <vCard:EMAIL rdf:parseType="Resource">
            <rdf:value>

```

```

    trevor.graham@ucl.ac.uk
  </rdf:value>
  <rdf:type rdf:resource="http://imc.org/vCard/3.0#internet"></rdf:type>
</vCard:EMAIL>
<vCard:ORG rdf:parseType="Resource">
  <vCard:Orgname>
    University College London
  </vCard:Orgname>
  <vCard:Orgunit>
    CoMPLEX
  </vCard:Orgunit>
</vCard:ORG>
</dc:creator>
</rdf:Description>
<!-- Created on -->
<dcterms:created rdf:parseType="Resource">
  <dcterms:W3CDTF>
    2004-1-26
  </dcterms:W3CDTF>
</dcterms:created>
<!-- Model information -->
<rdf:Description rdf:about="#Gprotein_controlled_glycogen_production">
  <!-- Model contents -->
  <dc:title>
    A three moduli model of glycogen production in hepatic cells.
  </dc:title>
  <!-- Model comment -->
  <cmeta:comment rdf:parseType="Resource">
    <rdf:value>
      This is the CellML description of a three moduli model of hormone induced glycogenolysis in hepatic cells. The three moduli are: g-protein signalling, based on a model by Riccobene et al 1999, the phospholipase C pathway, based on a model by Hofer et al 1999 and glucose-glycogen conversion, using a Gall's et al 2000 modification to the Cardenas and Goldbeter model 1996. An excellent review of hormone induced hepatic glycogenolysis is the article by Bollen et. al. referenced here.
    </rdf:value>
    <dc:creator rdf:parseType="Resource">
      <vCard:FN>
        Trevor Graham
      </vCard:FN>
    </dc:creator>
  </cmeta:comment>
  <!-- Bollen article meta-data -->
  <bqs:reference rdf:parseType="Resource">
    <bqs:JournalArticle rdf:parseType="Resource">
      <dc:creator>
        <rdf:Seq>
          <rdf:li rdf:parseType="Resource">
            <bqs:Person rdf:parseType="Resource">
              <vCard:N rdf:parseType="Resource">
                <vCard:Family>
                  Bollen
                </vCard:Family>
                <vCard:Given>
                  Matthieu
                </vCard:Given>
              </vCard:N>
            </bqs:Person>
          </rdf:li>
          <rdf:li rdf:parseType="Resource">

```

```

    <bqs:Person rdf:parseType="Resource">
      <vCard:N rdf:parseType="Resource">
        <vCard:Family>
          Keppans
        </vCard:Family>
        <vCard:Given>
          Stefan
        </vCard:Given>
      </vCard:N>
    </bqs:Person>
  </rdf:li>
  <rdf:li rdf:parseType="Resource">
    <bqs:Person rdf:parseType="Resource">
      <vCard:N rdf:parseType="Resource">
        <vCard:Family>
          Stalmans
        </vCard:Family>
        <vCard:Given>
          Willy
        </vCard:Given>
      </vCard:N>
    </bqs:Person>
  </rdf:li>
</rdf:Seq>
</dc:creator>
<dc:title>
  Specific features of glycogen metabolism in the liver
</dc:title>
<dcterms:issued rdf:parseType="Resource">
  <dcterms:W3CDTF>
    1998-11-15
  </dcterms:W3CDTF>
</dcterms:issued>
<bqs:Journal rdf:parseType="Resource">
  <dc:title>
    Biochemical Journal
  </dc:title>
</bqs:Journal>
<bqs:volume>
  336
</bqs:volume>
<bqs:first_page>
  19
</bqs:first_page>
<bqs:last_page>
  31
</bqs:last_page>
</bqs:JournalArticle>
</bqs:reference>
</rdf:Description>
<!-- Cell type -->
<cmeta:species>
  Mammalia
</cmeta:species>
<cmeta:bio_entity>
  Hepatocyte
</cmeta:bio_entity>
</rdf:RDF>
<!-- ===== Units description ===== -->

```

```

<units name="micromolar">
  <unit prefix="micro" units="mole"></unit>
  <unit exponent="-1" units="litre"></unit>
</units>
<units name="micromolarrate">
  <unit prefix="micro" units="mole"></unit>
  <unit exponent="-1" units="litre"></unit>
  <unit exponent="-1" units="seconds"></unit>
</units>
<units name="first_order_rate_constant">
  <unit exponent="-1" units="second"></unit>
</units>
<!-- ===== Model description ===== -->
<!-- "environment" declares variables used by all or most of the components -->
<component name="environment">
  <variable cmeta:id="time" name="t" public_interface="out" units="seconds"></variable>
</component>
<!-- G-protein signalling moduli -->
<component cmeta:id="g_protein_signal" name="g_protein_signal">
  <!-- Component comment -->
  <rdf:RDF xmlns:bqs="http://www.cellml.org/bqs/1.0#" xmlns:dc="http://purl.org/dc/elements/1.1/"
xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xm
lns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#">
  <!-- Component information -->
  <rdf:Description rdf:about="#g-protein_signal">
  <!-- Component contents -->
  <dc:title>
    G-protein activation by extra-cellular ligands based on the model by Riccobene et al.
  </dc:title>
  <cmeta:comment rdf:parseType="Resource">
  <rdf:value>
    This is the CellML description of G-protein activation by extra-cellular ligands. The descri
    ption is derived from a model by Riccobene et al 1999. The extra-cellular ligand concetration is inp
    utted and the model computes the activated G-protein concentration.
  </rdf:value>
  <dc:creator rdf:parseType="Resource">
  <vCard:FN>
    Trevor Graham
  </vCard:FN>
  </dc:creator>
  </cmeta:comment>
  <!-- article meta-data -->
  <bqs:reference rdf:parseType="Resource">
  <bqs:JournalArticle rdf:parseType="Resource">
  <dc:creator>
  <rdf:Seq>
  <rdf:li rdf:parseType="Resource">
  <bqs:Person rdf:parseType="Resource">
  <vCard:N rdf:parseType="Resource">
  <vCard:Family>
    Riccobene
  </vCard:Family>
  <vCard:Given>
    Todd
  </vCard:Given>
  </vCard:N>
  </bqs:Person>
  </rdf:li>
  <rdf:li rdf:parseType="Resource">

```

```

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        </vCard:Given>
      </vCard:N>
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  Modeling Activation and Desensitization of G-Protein Coupled Receptors Provides Insight into Ligand Efficacy
</dc:title>
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    1999-10-21
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  <dc:title>
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</bqs:first_page>
<bqs:last_page>
  222
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<variable cmeta:id="L" name="L" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#L">
      Extracellular ligand concentration
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</variable>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#R">
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    </rdf:Description>
  </rdf:RDF>
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<variable cmeta:id="Ra" name="Ra" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ra">
      Active G-protein linked receptor concetration
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Rds" name="Rds" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Rds">
      Desensitized receptor concetration
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="C" name="C" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#C">
      Relaxed ligand-receptor concetration
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Ca" name="Ca" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ca">
      Active ligand-receptor concetration
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Cds" name="Cds" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ca">
      Desnsitized ligand-receptor concetration
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="G" name="G" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#G">
      Relaxed G-protein concetration
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Ga" name="Ga" private_interface="out" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ga">
      Active G-protein concetration
    </rdf:Description>
  </rdf:RDF>
</variable>
<!-- Parameters -->
<variable cmeta:id="Kact" name="Kact" public_interface="out" units="dimensionless">

```



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<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#Kact">
    receptor activation equilibrium constant
  </rdf:Description>
</rdf:RDF>
</variable>
<variable cmeta:id="kfR" name="kfR" public_interface="out" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#kfR">
      receptor activation forward rate constant
    </rdf:Description>
  </rdf:RDF>
</variable>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#kf">
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    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="kr" name="kr" public_interface="out" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#kr">
      complex dissociation rate constant
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="kf2" name="kf2" public_interface="out" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#kf2">
      desensitized complex formation rate constant
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="kr2" name="kr2" public_interface="out" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#kr2">
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    </rdf:Description>
  </rdf:RDF>
</variable>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#alpha">
      affinity of receptor to switch between active and relaxed sites
    </rdf:Description>
  </rdf:RDF>
</variable>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#ka">
      g-protein activation rate constant
    </rdf:Description>
  </rdf:RDF>
</variable>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#ki">
      g-protein relaxation rate constant

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    </rdf:Description>
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  </rdf:RDF>
</variable>
<!-- Reaction kinetics -->
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      </bvar>
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    <apply>
      <times></times>
      <ci>
        kf
      </ci>
      <ci>
        L
      </ci>
      <ci>
        R
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        <ci>
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        </ci>
        <ci>
          C
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</apply>

```

```

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    </ci>
    <ci>
      Kact
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      Ca
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    <ci>
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</apply>
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          C
        </ci>
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```

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kfR
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    L
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```

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      </bvar>
      <apply>
        <ci>
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```

```

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    G
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          C

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Ra

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                <ci>
                    kf2
                </ci>
                <ci>
                    L
                </ci>
                <ci>
                    Rds
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        </apply>
    </mathml:math>
</component>
<!-- IP3 activation -->
<component cmeta:id="IP3_activation" name="IP3_activation">
    <!-- Component comment -->
    <rdf:RDF xmlns:bqs="http://www.cellml.org/bqs/1.0#" xmlns:dc="http://purl.org/dc/elements/1.1/"
xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xm
lns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#">

```

```

<!-- Component information -->
<rdf:Description rdf:about="#IP3_activation">
  <!-- Component contents -->
  <dc:title>
    G-protein activation of IP3.
  </dc:title>
  <cmeta:comment rdf:parseType="Resource">
    <rdf:value>
      This is the CellML description of IP3 activation by stimulated G-proteins. The concentration
      of IP3 is assumed to be proportional to the concentration of G-protein with a constant decay rate.
    </rdf:value>
    <dc:creator rdf:parseType="Resource">
      <vCard:FN>
        Trevor Graham
      </vCard:FN>
    </dc:creator>
  </cmeta:comment>
</rdf:Description>
</rdf:RDF>
<!-- variables -->
<variable cmeta:id="I" name="I" public_interface="out" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#I">
      concentration of IP3
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Ga" name="Ga" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ga">
      concentration of activated G-protein
    </rdf:Description>
  </rdf:RDF>
</variable>
<!-- parameters -->
<variable cmeta:id="kg" name="kg" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#kg">
      rate constant for formation of IP3 from activated G-proteins
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="kd" name="kd" units="micromolarrate">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#kd">
      constant degredation rate of g-proteins
    </rdf:Description>
  </rdf:RDF>
</variable>
<mathml:math xmlns="http://www.w3.org/1998/Math/MathML">
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    <eq></eq>
  </apply>
  <diff></diff>
  <bvar>
    <ci>
      t
    </ci>
  </bvar>
</mathml:math>

```

```

</bvar>
<apply>
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    I
  </ci>
</apply>
</apply>
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  <apply>
    <times></times>
    <ci>
      kg
    </ci>
    <ci>
      Ga
    </ci>
  </apply>
  <ci>
    kd
  </ci>
</apply>
</mathml:math>
</component>
<!-- Phospholipase C pathway -->
<component cmeta:id="phospholipaseC_hofer" name="phospholipaseC_hofer">
  <!-- Component comment -->
  <rdf:RDF xmlns:bqs="http://www.cellml.org/bqs/1.0#" xmlns:dc="http://purl.org/dc/elements/1.1/"
xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xm
lns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#">
  <!-- Component information -->
  <rdf:Description rdf:about="#phospholipaseC_hofer">
    <!-- Component contents -->
    <dc:title>
      Phospholipase C pathway model of Hofer 1999.
    </dc:title>
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        This is the CellML description of the phospholipase C pathway model by Hofer 1999. The model
        takes the concentration of IP3 as an input and computes the induced concentration of cytosolic Ca2+.
      </rdf:value>
      <dc:creator rdf:parseType="Resource">
        <vCard:FN>
          Trevor Graham
        </vCard:FN>
        </dc:creator>
      </cmeta:comment>
      <!-- article meta-data -->
      <bqs:reference rdf:parseType="Resource">
        <bqs:JournalArticle rdf:parseType="Resource">
          <dc:creator>
            <rdf:Seq>
              <rdf:li rdf:parseType="Resource">
                <bqs:Person rdf:parseType="Resource">
                  <vCard:N rdf:parseType="Resource">
                    <vCard:Family>
                      Hofer

```

```

        </vCard:Family>
        <vCard:Given>
            Thomas
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    </vCard:N>
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</rdf:li>
</rdf:Seq>
</dc:creator>
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    Model of Intercellular Calcium Oscillations in Hepatocytes: Synchroniaztion of Heterogeneous
s Cells
</dc:title>
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    </dcterms:W3CDTF>
</dcterms:issued>
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    <dc:title>
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    </dc:title>
</bqs:Journal>
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</bqs:volume>
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    1256
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</bqs:reference>
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<!-- variables -->
<variable cmeta:id="I" name="I" public_interface="in" units="micromolar">
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
        <rdf:Description rdf:about="#I">
            concentration of IP3
        </rdf:Description>
    </rdf:RDF>
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<variable cmeta:id="Z" name="Z" public_interface="out" units="micromolar">
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
        <rdf:Description rdf:about="#Z">
            concentration of cytosolic Ca2+
        </rdf:Description>
    </rdf:RDF>
</variable>
<variable cmeta:id="W" name="W" public_interface="out" units="micromolar">
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
        <rdf:Description rdf:about="#W">
            whole cell Ca2+ concentration
        </rdf:Description>
    </rdf:RDF>
</variable>
<!-- parameters -->

```

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<variable cmeta:id="rho" name="rho" units="dimensionless">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#rho">
      ratio area of plasma membrane to effective cytosolic calcium capacity
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="alpha" name="alpha" units="dimensionless">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#alpha">
      ratio of area of ER to area of plasma membrane
    </rdf:Description>
  </rdf:RDF>
</variable>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#beta">
      ratio of effective calcium capacity of ER to effective cytosolic calcium capacity
    </rdf:Description>
  </rdf:RDF>
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<variable cmeta:id="k1" name="k1" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#k1">
      IP3 mediated release of Ca2+ from ER rate constant
    </rdf:Description>
  </rdf:RDF>
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<variable cmeta:id="k2" name="k2" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#k2">
      small leak flux of Ca2+ into cytosol rate constant
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  </rdf:RDF>
</variable>
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<variable cmeta:id="dp" name="dp" units="micromolar"></variable>
<variable cmeta:id="d1" name="d1" units="micromolar"></variable>
<variable cmeta:id="d2" name="d2" units="micromolar"></variable>
<variable cmeta:id="d3" name="d3" units="micromolar"></variable>
<variable cmeta:id="v3" name="v3" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#v3">
      Ca2+ uptake from cytosol into ER rate constant
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="K3" name="K3" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K3">
      Michaelis constant for Ca2+ uptake from cytosol into ER
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="v4" name="v4" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#v4">
      Ca2+ flux out of cell across cell membrane rate constant
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  </rdf:RDF>
</variable>

```

```

</rdf:RDF>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K4">
      Michaelis constant for Ca2+ flux out of cell across cell membrane
    </rdf:Description>
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<variable cmeta:id="vc" name="vc" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#vc">
      Maximal rate for IP3 induced Ca2+ flux into cell across cell membrane
    </rdf:Description>
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<variable cmeta:id="K0" name="K0" units="micromolar">
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    <rdf:Description rdf:about="#K0">
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</component>
<!-- Gall's Ca2+ extension -->
<component cmeta:id="calcium_gall" name="calcium_gall">
  <!-- Component comment -->
  <rdf:RDF xmlns:bqs="http://www.cellml.org/bqs/1.0#" xmlns:dc="http://purl.org/dc/elements/1.1/"
xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xm
lns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#">
  <!-- Component information -->
  <rdf:Description rdf:about="#calcium_gall">
  <!-- Component contents -->
  <dc:title>
    Gall 2000 calcium extension to the Cardenas and Goldbeter model.
  </dc:title>
  <cmeta:comment rdf:parseType="Resource">
  <rdf:value>
    This is the CellML description of Gall's 2000 calcium control extension to the Cardenas and
    Goldbeter model of glycogen production. The model computes the rate parameters of glycogen phosphory
    lase using the cytosolic Ca2+ concentration.
  </rdf:value>
  <dc:creator rdf:parseType="Resource">
  <vCard:FN>
    Trevor Graham
  </vCard:FN>
  </dc:creator>
  </cmeta:comment>
  <!-- article meta-data -->
  <bqs:reference rdf:parseType="Resource">

```

```

<bqs:JournalArticle rdf:parseType="Resource">
  <dc:creator>
    <rdf:Seq>
      <rdf:li rdf:parseType="Resource">
        <bqs:Person rdf:parseType="Resource">
          <vCard:N rdf:parseType="Resource">
            <vCard:Family>
              Gall
            </vCard:Family>
            <vCard:Given>
              David
            </vCard:Given>
          </vCard:N>
        </bqs:Person>
      </rdf:li>
      <rdf:li rdf:parseType="Resource">
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          <vCard:N rdf:parseType="Resource">
            <vCard:Family>
              Baus
            </vCard:Family>
            <vCard:Given>
              Erika
            </vCard:Given>
          </vCard:N>
        </bqs:Person>
      </rdf:li>
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            </vCard:Family>
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              Genevieve
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          </vCard:N>
        </bqs:Person>
      </rdf:li>
    </rdf:Seq>
  </dc:creator>
  <dc:title>
    Activation of the Liver Glycogen Phosphorylase by Ca2+ Oscillations: a Theoretical Study
  </dc:title>
  <dcterms:issued rdf:parseType="Resource">
    <dcterms:W3CDTF>
      2000-12-21
    </dcterms:W3CDTF>
  </dcterms:issued>
  <bqs:Journal rdf:parseType="Resource">
    <dc:title>
      Journal of Theoretical Biology
    </dc:title>
  </bqs:Journal>
  <bqs:volume>
    207
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  <bqs:first_page>
    445

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    </bqs:first_page>
    <bqs:last_page>
      454
    </bqs:last_page>
  </bqs:JournalArticle>
</bqs:reference>
</rdf:Description>
</rdf:RDF>
<!-- variables -->
<variable cmeta:id="Z" name="Z" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Z">
      concentration of cytosolic Ca2+
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="V1" name="V1" public_interface="out" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#V1">
      maximum rate of glycogen phosphorylase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="K1" name="K1" public_interface="out" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K1">
      Michaelis constant for glycogen phosphorylase
    </rdf:Description>
  </rdf:RDF>
</variable>
<!-- parameters -->
<variable cmeta:id="K11" name="K11" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K11">
      Michaelis constant for activation of phosphorylase kinase by Ca2+
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="VM1" name="VM1" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#VM1">
      Maximum activation rate of phosphorylase kinase by Ca2+
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Ka5" name="Ka5" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ka5">
      Further activation constant for phosphorylase kinase activation by Ca2+
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Ka6" name="Ka6" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ka6">
      Activation constant for phosphorylase kinase Ca2+
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  </rdf:RDF>
</variable>

```



```

<variable cmeta:id="gamma" name="gamma" units="dimensionless">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#gamma">
      Factor for rate increase of phosphorylase kinase due to Ca2+ activation
    </rdf:Description>
  </rdf:RDF>
</variable>
<mathml:math xmlns="http://www.w3.org/1998/Math/MathML">
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</component>
<!-- Cardenas and Goldbeter glycogen production -->
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  <!-- Component comment -->
  <rdf:RDF xmlns:bqs="http://www.cellml.org/bqs/1.0#" xmlns:dc="http://purl.org/dc/elements/1.1/"
xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xm
lns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#">
    <!-- Component information -->
    <rdf:Description rdf:about="#glycogen_cardenas">
      <!-- Component contents -->
      <dc:title>
        Cardenas and Goldbeter model of glycogen production in hepatic cells.
      </dc:title>
      <cmeta:comment rdf:parseType="Resource">
        <rdf:value>
          This is the CellML description of Cardenas and Goldbeter's model of glycogen production in h
          epatic cells. The concentration of active glycogen phosphorylase and synthase is computed.
        </rdf:value>
      <dc:creator rdf:parseType="Resource">
        <vCard:FN>
          Trevor Graham
        </vCard:FN>
      </dc:creator>
    </cmeta:comment>
  <!-- Article meta-data-->

```

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  <bqs:JournalArticle rdf:parseType="Resource">
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              <vCard:Given>
                Maria
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      The Glucose-induced Switch Between Glycogen Phosphorylase and Glycogen Synthase in the Liver: Outlines of a Theoretical Approach
    </dc:title>
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      </dcterms:W3CDTF>
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      </dc:title>
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    <rdf:Description rdf:about="#V1">
      maximum rate of glycogen phosphorylase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="K1" name="K1" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K1">
      Michaelis constant for glycogen phosphorylase
    </rdf:Description>
  </rdf:RDF>
</variable>
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  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#P">
      Concentration of active glycogen phosphorylase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="S" name="S" public_interface="out" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#S">
      Concentration of active glycogen synthase
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  </rdf:RDF>
</variable>
<variable cmeta:id="Y" name="Y" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Y">
      Concentration of glucoses-6-phosphate
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="U" name="U" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#U">
      Concentration of glucose
    </rdf:Description>
  </rdf:RDF>
</variable>
<!-- parameters -->
<variable cmeta:id="K2" name="K2">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K2">
      Michaelis constant for phosphorylase phosphatase activation by glucose
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="VM2" name="VM2">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#VM2">
      Maximum rate of phosphorylase phosphatase activation by glucose
    </rdf:Description>
  </rdf:RDF>
</variable>

```

```

<variable cmeta:id="Ka1" name="Ka1">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ka1">
      Activation constant for futher activation phosphorylase phosphatase by glucose
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Ka2" name="Ka2">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ka2">
      Activation constant for phosphorylase phosphatase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="alpha" name="alpha">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#alpha">
      Amplification factor for rate of activated phosphorylase phosphatase by glucose
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="K3" name="K3">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K3">
      Michaelis constant for synthase phosphatase activation by glucose-6-phosphate
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="VM3" name="VM3">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#VM3">
      Maximum rate of synthase phosphatase activation by glucose-6-phosphate
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Ka4" name="Ka4">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Ka4">
      Activation constant for synthase phosphatase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="beta" name="beta">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#beta">
      Amplification factor for rate of activated synthase phosphatase by glucose-6-phosphate
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="K4" name="K4">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#K4">
      Michaelis constant for synthase phosphatase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="V4" name="V4">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#V4">

```

```

Maximum rate of synthase phosphatase
</rdf:Description>
</rdf:RDF>
</variable>
<mathml:math xmlns="http://www.w3.org/1998/Math/MathML">
<apply cmeta:id="dP">
<eq></eq>
<apply>
<diff></diff>
<bvar>
<ci>
t
</ci>
</bvar>
<apply>
<ci>
P
</ci>
</apply>
</apply>
<apply>
<minus></minus>
<apply>
<divide></divide>
<apply>
<times></times>
<ci>
V1
</ci>
<apply>
<minus></minus>
<cn>
1
</cn>
<ci>
P
</ci>
</apply>
</apply>
<apply>
<plus></plus>
<ci>
K1
</ci>
<cn>
1
</cn>
<apply>
<minus></minus>
<ci>
P
</ci>
</apply>
</apply>
</apply>
<apply>
<divide></divide>
<apply>
<times></times>

```

```

<ci>
  VM2
</ci>
<apply>
  <plus></plus>
  <cn>
    1
  </cn>
  <apply>
    <divide></divide>
    <apply>
      <plus></plus>
      <cn>
        1
      </cn>
    <apply>
      <times></times>
      <ci>
        alpha
      </ci>
      <ci>
        U
      </ci>
    </apply>
  </apply>
  <apply>
    <plus></plus>
    <ci>
      Ka1
    </ci>
    <ci>
      U
    </ci>
  </apply>
</apply>
<apply>
  <plus></plus>
  <apply>
    <divide></divide>
    <ci>
      K2
    </ci>
    <apply>
      <plus></plus>
      <cn>
        1
      </cn>
    <apply>
      <divide></divide>
      <ci>
        U
      </ci>
      <ci>
        Ka2
      </ci>
    </apply>
  </apply>
</apply>

```

```

    </apply>
    <ci>
    P
    </ci>
  </apply>
</apply>
</apply>
</mathml:math>
<mathml:math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply cmeta:id="dS">
    <eq></eq>
    <apply>
      <diff></diff>
      <bvar>
        <ci>
        t
        </ci>
      </bvar>
      <apply>
        <ci>
        S
        </ci>
      </apply>
    </apply>
    <apply>
      <minus></minus>
      <apply>
        <divide></divide>
        <apply>
          <times></times>
          <ci>
            VM3
          </ci>
          <apply>
            <plus></plus>
            <cn>
              1
            </cn>
          </apply>
        </divide></divide>
        <apply>
          <times></times>
          <ci>
            beta
          </ci>
          <ci>
            Y
          </ci>
          <ci>
            K1
          </ci>
        </apply>
      </times></times>
      <apply>
        <plus></plus>
        <ci>
          Ka3

```



```

    </ci>
    <ci>
    Y
    </ci>
  </apply>
  <apply>
    <plus></plus>
    <ci>
    K1
    </ci>
    <ci>
    Y
    </ci>
  </apply>
</apply>
<apply>
  <minus></minus>
  <cn>
  1
  </cn>
  <ci>
  U
  </ci>
</apply>
</apply>
<apply>
  <plus></plus>
  <apply>
    <divide></divide>
    <ci>
    K3
    </ci>
  <apply>
    <plus></plus>
    <cn>
    1
    </cn>
  <apply>
    <divide></divide>
    <ci>
    Y
    </ci>
    <ci>
    Ka4
    </ci>
  </apply>
</apply>
</apply>
<cn>
  1
  </cn>
  <apply>
    <minus></minus>
    <ci>
    U
    </ci>
  </apply>

```

```

    </apply>
  </apply>
  <apply>
    <divide></divide>
    <apply>
      <times></times>
      <ci>
        V4
      </ci>
      <ci>
        U
      </ci>
    </apply>
    <apply>
      <plus></plus>
      <ci>
        K4
      </ci>
      <ci>
        U
      </ci>
    </apply>
  </apply>
</mathml:math>
</component>
<!-- Glycogen conversion -->
<component cmeta:id="glycogen_conversion" name="glycogen_conversion">
  <!-- Component comment -->
  <rdf:RDF xmlns:bqs="http://www.cellml.org/bqs/1.0#" xmlns:dc="http://purl.org/dc/elements/1.1/"
xmlns:dcterms="http://purl.org/dc/terms/" xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xm
lns:vCard="http://www.w3.org/2001/vcard-rdf/3.0#">
  <!-- Component information -->
  <rdf:Description rdf:about="#glycogen_conversion">
    <!-- Component contents -->
    <dc:title>
      Glucose - glycogen conversion.
    </dc:title>
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        This is the CellML description of the conversion between glucose and glycogen. The conversio
n rate is proportional to the relative concentrations of the active glycogen phosphorylase and synth
ase. The concentration of glucose-6-phosphate is also computed. The concentration of G6P is proporti
onal to the concentration of glucose with a constant rate of degradation.
      </rdf:value>
      <dc:creator rdf:parseType="Resource">
        <vCard:FN>
          Trevor Graham
        </vCard:FN>
      </dc:creator>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>
<variable cmeta:id="P" name="P" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#P">
      Concentration of active glycogen phosphorylase
    </rdf:Description>

```

```

</rdf:RDF>
</variable>
<variable cmeta:id="S" name="S" public_interface="in" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#S">
      Concentration of active glycogen synthase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Y" name="Y" public_interface="out" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Y">
      Concentration of glucoses-6-phosphate
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="U" name="U" public_interface="out" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#U">
      Concentration of glucose
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="Q" name="Q" public_interface="out" units="micromolar">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#Q">
      Concentration of glycogen
    </rdf:Description>
  </rdf:RDF>
</variable>
<!-- parameters -->
<variable cmeta:id="VUf" name="VUf" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#VUf">
      Maximum rate of glycogen phosphorylase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="VUb" name="VUb" units="first_order_rate_constant">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#VUb">
      Maximum rate of glycogen synthase
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="m" name="m" units="dimensionless">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#m">
      Number of molecules of glucose in a glycogen molecule
    </rdf:Description>
  </rdf:RDF>
</variable>
<variable cmeta:id="tau" name="tau" units="dimensionless">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#tau">
      Time lag for glucose-6-phosphate concentration
    </rdf:Description>
  </rdf:RDF>
</variable>

```

```

<mathml:math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply cmeta:id="dY">
    <eq></eq>
    <apply>
      <diff></diff>
      <bvar>
        <ci>
          t
        </ci>
      </bvar>
      <apply>
        <ci>
          Y
        </ci>
      </apply>
    </apply>
    <apply>
      <divide></divide>
      <apply>
        <minus></minus>
        <ci>
          U
        </ci>
        <ci>
          Y
        </ci>
      </apply>
      <ci>
        tau
      </ci>
    </apply>
  </apply>
</mathml:math>
<mathml:math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply cmeta:id="dU">
    <eq></eq>
    <apply>
      <diff></diff>
      <bvar>
        <ci>
          t
        </ci>
      </bvar>
      <apply>
        <ci>
          U
        </ci>
      </apply>
    </apply>
    <apply>
      <minus></minus>
      <apply>
        <times></times>
        <ci>
          VUf
        </ci>
        <ci>
          P
        </ci>
      </apply>
    </apply>
  </apply>
</mathml:math>

```

```

</apply>
<apply>
  <times></times>
  <ci>
    VUb
  </ci>
  <ci>
    S
  </ci>
</apply>
</apply>
</mathml:math>
<mathml:math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply cmeta:id="dQ">
    <eq></eq>
    <apply>
      <diff></diff>
      <bvar>
        <ci>
          t
        </ci>
      </bvar>
      <apply>
        <ci>
          Q
        </ci>
        <ci>
          t
        </ci>
      </apply>
    </apply>
    <apply>
      <plus></plus>
      <apply>
        <minus></minus>
        <apply>
          <times></times>
          <ci>
            VUf
          </ci>
          <ci>
            P
          </ci>
        </apply>
      </apply>
    </apply>
    <apply>
      <times></times>
      <ci>
        VUb
      </ci>
      <ci>
        S
      </ci>
    </apply>
  </apply>
</mathml:math>
</component>

```

```

<connection cmeta:id="con_Ga">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#con_Ga">
      Connection between g-protein signalling component and IP3 activation component by activated G-
protein
    </rdf:Description>
  </rdf:RDF>
  <map_components component_1="g_protein_signal" component_2="IP3_activation"></map_components>
  <map_variables variable_1="Ga" variable_2="Ga"></map_variables>
</connection>
<connection cmeta:id="con_IP3">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#con_IP3">
      Connection between IP3 activation component and phospholipase C pathway component by IP3 conce
ntration
    </rdf:Description>
  </rdf:RDF>
  <map_components component_1="IP3_activation" component_2="phospholipaseC_hofer"></map_components
>
  <map_variables variable_1="I" variable_2="I"></map_variables>
</connection>
<connection cmeta:id="con_Ca">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#con_Ca">
      Connection between phospholipase C pathway component and calcium control of glycogen phosphory
lase component by Ca2+ concentration
    </rdf:Description>
  </rdf:RDF>
  <map_components component_1="phospholipaseC_hofer" component_2="Calcium_gall"></map_components>

  <map_variables variable_1="Z" variable_2="Z"></map_variables>
</connection>
<connection cmeta:id="con_gly_phos">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#con_gly_phos">
      Connection between calcium control of glycogen phosphorylase component and glycogen synthase/p
hosphorylase activation
    </rdf:Description>
  </rdf:RDF>
  <map_components component_1="calcium_gall" component_2="glycogen_cardenas"></map_components>
  <map_variables variable_1="V1" variable_2="V1"></map_variables>
  <map_variables variable_1="K1" variable_2="K1"></map_variables>
</connection>
<connection cmeta:id="con_gly_conv">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#">
      Connection between glycogen phosphorylase component and glucose - glycogen synthase
    </rdf:Description>
  </rdf:RDF>
  <map_components component_1="glycogen_cardenas" component_2="glycogen_conversion"></map_componen
ts>
  <map_variables variable_1="P" variable_2="P"></map_variables>
  <map_variables variable_1="S" variable_2="S"></map_variables>
  <map_variables variable_1="Y" variable_2="Y"></map_variables>
  <map_variables variable_1="U" variable_2="U"></map_variables>
</connection>
</model>

```

12.3 sbML visualisation

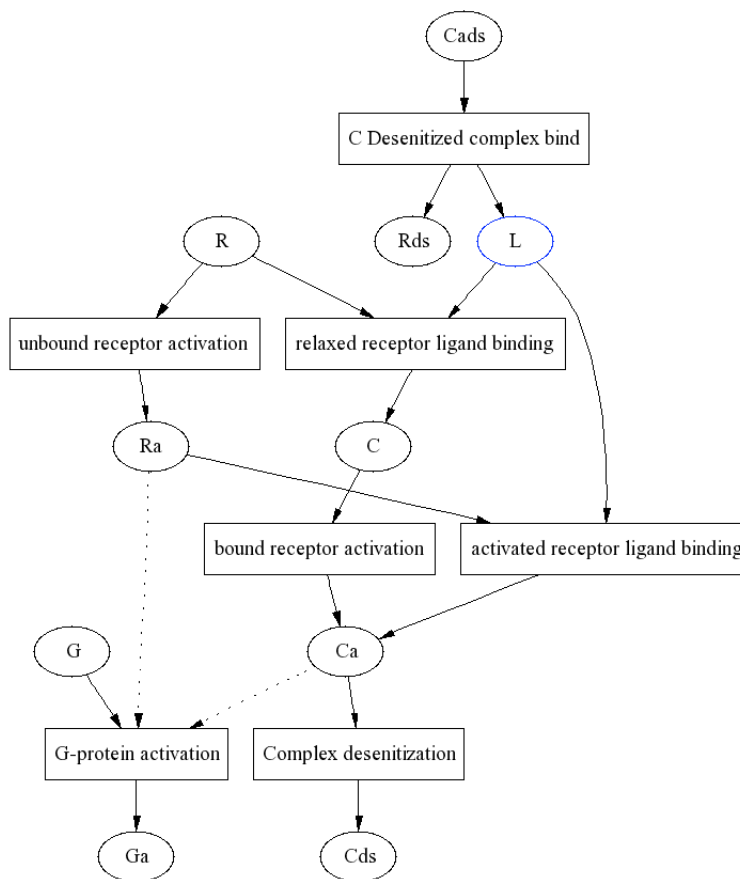


Figure 10: Visualisation generated from the sbML code for the g-protein linked receptor using the sbML validation tools