

```
<?xml version="1.0"?>
```

```
<!--
```

```
FILE : bi_egf_pathway_1999_raw.xml
```

```
CREATED : 11 November 2000
```

```
LAST MODIFIED : 9th April 2003
```

```
AUTHOR : Melanie Nelson  
        Physiome Sciences, Inc.
```

```
DESCRIPTION : This file contains a CellML description of the EGF pathway  
              model from Bhalla and Iyengar.
```

```
CHANGES:
```

```
25/05/2002 - AAC - Updated metadata to conform to the 16/1/02 CellML Metadata  
              1.0 Specification.
```

```
08/03/2002 - AAC - Fixed connection/variable errors.
```

```
22/07/2002 - CML - Added more metadata.
```

```
09/04/2003 - AAC - Added publication date information.
```

```
24/12/2004 - CML - Corrected model errors - there are still more but I don't really understand
```

```
-->
```

```
<model name="bi_egf_pathway_1999" cmeta:id="bi_egf_pathway_1999" xmlns="http://www.cellml.org
```

```
<!--
```

```
This RDF block contains metadata that applies to the entire model.  
The CellML development team recommends that RDF metadata about an element  
be included as a child of the element. However, the RDF spec does not  
require this. Metadata can be placed anywhere in the model document, or  
even in another document, as long as the <rdf:Description> elements contain  
about attributes that refer to the correct resource. Because this is an  
example, reasonably extensive metadata has been included. The CellML  
development team recommends that model authors include as much metadata  
as possible because this will make it easier for others to find and  
use the model. However, no metadata is required.
```

```
-->
```

```
<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:bqgs="http://www.cel
```

```
<!--
```

```
The following RDF block contains metadata that applies to this document  
as a whole, as indicated by the empty about attribute on the  
<rdf:Description> element.
```

```
-->
```

```
<rdf:Description rdf:about="">
```

```
<!-- The Human Readable Name metadata. -->
```

```
<dc:title>
```

```
Epidermal growth factor stimulation of mitogen-associated protein  
kinase and activation of Ras
```

```
</dc:title>
```

```
<!--
```

```
The Model Builder metadata. The CellML spec recommends that the  
creator element be used to indicate the person who coded the model  
into CellML, rather than the person who originally developed the  
model. The information about the person who originally developed  
the model is available via the reference metadata.
```

```
-->
```

```
<dc:creator rdf:parseType="Resource">
```

```
<vCard:N rdf:parseType="Resource">
```

```

    <vCard:Family>Nelson</vCard:Family>
    <vCard:Given>Melanie</vCard:Given>
</vCard:N>
<vCard:EMAIL rdf:parseType="Resource">
    <rdf:value>mnelson@physiome.com</rdf:value>
    <rdf:type rdf:resource="http://imc/org/vCard/3.0#internet" />
</vCard:EMAIL>
<vCard:ORG rdf:parseType="Resource">
    <vCard:Orgname>Physiome Sciences, Inc.</vCard:Orgname>
</vCard:ORG>
<vCard:ADR rdf:parseType="Resource">
    <vCard:Extadd>Physiome Sciences, Inc.</vCard:Extadd>
    <vCard:Street>150 College Road West</vCard:Street>
    <vCard:Locality>Princeton</vCard:Locality>
    <vCard:Region>NJ</vCard:Region>
    <vCard:Country>USA</vCard:Country>
    <vCard:Pcode>08540-6604</vCard:Pcode>
</vCard:ADR>
<vCard:TEL rdf:parseType="Resource">
    <rdf:value>1-609-987-1199</rdf:value>
    <rdf:type rdf:resource="http://imc/org/vCard/3.0#work" />
</vCard:TEL>
<vCard:TEL rdf:parseType="Resource">
    <rdf:value>1-609-987-9393</rdf:value>
    <rdf:type rdf:resource="http://imc/org/vCard/3.0#fax" />
</vCard:TEL>
</dc:creator>

<!--
    The Creation Date metadata. This is the date on which the model
    was coded into CellML, not the date on which it was originally
    created (if it was originally created in a different language)
    or the date on which it was published.
-->
<dcterms:created rdf:parseType="Resource">
    <dcterms:W3CDTF>2000-10-11</dcterms:W3CDTF>
</dcterms:created>

<!--
    The Modification History metadata. This is the list of modifications
    made to the CellML description of the model with the date the
    modifications were made and the name of the person(s) who made the
    changes.
-->
<cmeta:modification rdf:parseType="Resource">
    <rdf:value>
        Updated CellML to conform with the 10/8/2001 CellML Version 1.0
        Specification.
    </rdf:value>
    <dcterms:modified rdf:parseType="Resource">
        <dcterms:W3CDTF>2001-08-02</dcterms:W3CDTF>
    </dcterms:modified>
    <cmeta:modifier rdf:parseType="Resource">
        <vCard:N rdf:parseType="Resource">
            <vCard:Family>Cuellar</vCard:Family>
            <vCard:Given>Autumn</vCard:Given>
            <vCard:Other>A.</vCard:Other>
        </vCard:N>
        <vCard:ORG rdf:parseType="Resource">

```

```

    <vCard:Orgunit>The Bioengineering Institute</vCard:Orgunit>
    <vCard:Orgname>The University of Auckland</vCard:Orgname>
  </vCard:ORG>
  <vCard:EMAIL rdf:parseType="Resource">
    <rdf:value>a.cuellar@auckland.ac.nz</rdf:value>
    <rdf:type rdf:resource="http://imc/org/vCard/3.0#internet" />
  </vCard:EMAIL>
</cmeta:modifier>
</cmeta:modification>
</rdf:Description>

```

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```

The following metadata refers to the model itself, as indicated by the
reference to the ID "bi_egf_pathway_1999", which is declared on
the <model> element.

```

```
-->
```

```
<rdf:Description rdf:about="#bi_egf_pathway_1999">
```

```
<!-- A human readable name for the model. -->
```

```
<dc:title>Bhalla and Iyengar's EGF Pathway, 1999</dc:title>
```

```
<!-- A comment regarding the model. -->
```

```
<cmeta:comment rdf:parseType="Resource">
```

```
<rdf:value>
```

```

This is the CellML description of Bhalla and Iyengar's mathematical
model of the EGF pathway (1999).

```

```
</rdf:value>
```

```
<!-- The creator of the comment. -->
```

```
<dc:creator rdf:parseType="Resource">
```

```
<vCard:FN>Catherine Lloyd</vCard:FN>
```

```
</dc:creator>
```

```
</cmeta:comment>
```

```
<!-- Keyword(s) -->
```

```
<bqs:reference rdf:parseType="Resource">
```

```
<dc:subject rdf:parseType="Resource">
```

```
<bqs:subject_type>keyword</bqs:subject_type>
```

```
<rdf:value>signal transduction</rdf:value>
```

```
</dc:subject>
```

```
</bqs:reference>
```

```
<!--
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```

The CellML Metadata Specification recommends that bibliographic metadata
is used to provide information about the original model reference. The
"identifier" attribute on the "BibliographicReference" class provides an
elegant way to identify a cited reference using a database identifier
date, etc can be looked up on the database.

```

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```

```
<bqs:reference rdf:parseType="Resource">
```

```
<bqs:Pubmed_id>99105994</bqs:Pubmed_id>
```

```
<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>Bhalla</vCard:Family>
```

```
<vCard:Given>Upinder</vCard:Given>
```

```
<vCard:Other>S</vCard:Other>
```

such

```

        </vCard:N>
    </bqs:Person>
</rdf:li>
<rdf:li rdf:parseType="Resource">
    <bqs:Person rdf:parseType="Resource">
        <vCard:N rdf:parseType="Resource">
            <vCard:Family>Iyengar</vCard:Family>
            <vCard:Given>Ravi</vCard:Given>
        </vCard:N>
    </bqs:Person>
</rdf:li>
</rdf:Seq>
</dc:creator>
<dc:title>
    Emergent Properties of Networks of Biological Signaling Pathways
</dc:title>
<dcterms:issued rdf:parseType="Resource">
    <dcterms:W3CDTF>1999-01-15</dcterms:W3CDTF>
</dcterms:issued>
<bqs:Journal rdf:parseType="Resource">
    <dc:title>Science</dc:title>
</bqs:Journal>
<bqs:volume>283</bqs:volume>
<bqs:first_page>381</bqs:first_page>
<bqs:last_page>387</bqs:last_page>
</bqs:JournalArticle>
</bqs:reference>
</rdf:Description>
</rdf:RDF>

<!--
    We start the model definition with a definition of some named
    sets of units for use throughout the model.
-->
<units name="concentration_units">
    <unit prefix="milli" units="mole" />
    <unit units="litre" exponent="-1" />
</units>

<units name="rate_units">
    <unit units="concentration_units" />
    <unit units="second" exponent="-1" />
</units>

<units name="first_order_rate_constant_units">
    <unit units="second" exponent="-1" />
</units>

<units name="second_order_rate_constant_units">
    <unit units="concentration_units" exponent="-1" />
    <unit units="second" exponent="-1" />
</units>

<units name="third_order_rate_constant_units">
    <unit units="concentration_units" exponent="-2" />
    <unit units="second" exponent="-1" />
</units>

<!--

```

The environment component is used to declare variables that are used by all or most of the other components. Variables must be declared inside of a <component> element.

```
-->
<component name="environment">
  <variable name="time" public_interface="out" units="second" />
</component>

<!--
  The first set of elements define a subsystem that handles the
  formation of the active EGF-EGFR complex.
-->
<component name="EGF" cmeta:id="EGF">
  <!-- This block of metadata applies only to the EGF component. -->
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/
    <rdf:Description rdf:about="EGF">

      <!-- Human Readable Name metadata. -->
      <dc:title>epidermal growth factor</dc:title>

      <!--
        The Biological Entity metadata. This metadata has a
        different meaning than the alias metadata provided above,
        even though the two pieces of metadata happen to have the
        same value in this example. The <dc:title> element provides a human
        readable name for the component. The <cmeta:bio_entity> element
        provides information about the biological entity which the component
        is meant to represent.
      -->
      <cmeta:bio_entity>epidermal growth factor</cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

  <!--
    The initial_value attribute on a <variable> element declares a value of
    the variable when all of the model's independent variables have a value of
    0.0. It is anticipated that initial values and other model boundary
    conditions would typically be set in an external simulation configuration
    file.
  -->
  <variable name="EGF" public_interface="out" initial_value="0.0" units="concentration_units" />
  <variable name="delta_EGF" public_interface="in" units="rate_units" />
  <variable name="time" public_interface="in" units="second" />
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply><eq />
      <apply><diff />
        <bvar><ci> time </ci></bvar>
        <ci> EGF </ci>
      </apply>
      <ci> delta_EGF </ci>
    </apply>
  </math>
</component>

<component name="EGFR" cmeta:id="EGFR">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/
    <rdf:Description rdf:about="EGFR">
      <dc:title>epidermal growth factor receptor</dc:title>
```

```

    <meta:bio_entity>epidermal growth factor receptor</meta:bio_entity>
  </rdf:Description>
</rdf:RDF>

<variable name="EGFR" public_interface="out" initial_value="0.1667" units="concentration" />
<variable name="delta_EGFR" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci> time </ci></bvar>
      <ci> EGFR </ci>
    </apply>
    <ci> delta_EGFR </ci>
  </apply>
</math>
</component>

<component name="EGF_EGFR" meta:id="EGF_EGFR">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="EGF_EGFR">
      <dc:title>epidermal growth factor-receptor complex</dc:title>
      <meta:bio_entity>
        complex of epidermal growth factor and
        epidermal growth factor receptor
      </meta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

  <variable name="EGF_EGFR" public_interface="out" initial_value="0.0" units="concentration" />
  <variable name="delta1_EGF_EGFR" public_interface="in" units="rate_units" />
  <variable name="delta2_EGF_EGFR" public_interface="in" units="rate_units" />
  <variable name="time" public_interface="in" units="second" />

  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply><eq />
      <apply><diff />
        <bvar><ci> time </ci></bvar>
        <ci> EGF_EGFR </ci>
      </apply>
      <apply><plus />
        <ci> delta1_EGF_EGFR </ci>
        <ci> delta2_EGF_EGFR </ci>
      </apply>
    </apply>
  </math>
</component>

<component name="EGF_EGFR_Int" meta:id="EGF_EGFR_Int">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="EGF_EGFR_Int">
      <dc:title>
        internalized epidermal growth factor-receptor complex
      </dc:title>
      <meta:bio_entity>
        internalized fraction of complex of epidermal growth factor
      </meta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

```

```

    and epidermal growth factor receptor
  </cmeta:bio_entity>
</rdf:Description>
</rdf:RDF>

<variable name="EGF_EGFR_Int" public_interface="out" initial_value="0.0" units="concentra
<variable name="delta_EGF_EGFR_Int" public_interface="in" units="rate_units" />
<variable name="time" private_interface="in" units="second" />

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci> time </ci></bvar>
      <ci> EGF_EGFR_Int </ci>
    </apply>
    <ci> delta_EGF_EGFR_Int </ci>
  </apply>
</math>
</component>

<!--
  This component represents the binding reaction between EGF and EGFR.
-->
<component name="EGF_EGFR_bind_rxn" cmeta:id="EGF_EGFR_bind_rxn">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.or
    <rdf:Description rdf:about="EGF_EGFR_bind_rxn">
      <dc:title>EGF-EGFR binding reaction</dc:title>
    </rdf:Description>
  </rdf:RDF>

  <variable name="EGF" public_interface="in" units="concentration_units" />
  <variable name="EGFR" public_interface="in" units="concentration_units" />
  <variable name="EGF_EGFR" public_interface="in" units="concentration_units" />
  <variable name="delta_EGF" public_interface="out" units="rate_units" />
  <variable name="delta_EGFR" public_interface="out" units="rate_units" />
  <variable name="delta_EGF_EGFR" public_interface="out" units="rate_units" />

  <!--
    k_forward and k_reverse are the forward and reverse rate constants,
    respectively. They are not needed by any other component in the
    model, and therefore have no public or private interface
  -->
  <variable name="k_forward" initial_value="0.000007" units="second_order_rate_constant_un
  <variable name="k_reverse" initial_value="0.25" units="first_order_rate_constant_units" /

  <variable name="r" units="rate_units" />

  <!--
    This reaction is reversible. The direction attributes on the role
    elements are also omitted in this example. The roles of the participants
    are all assumed to be for the default direction, i.e., "forward".
  -->
  <reaction reversible="yes">
    <variable_ref variable="EGF">
      <role role="reactant" delta_variable="delta_EGF" stoichiometry="1" />
    </variable_ref>
    <variable_ref variable="EGFR">
      <role role="reactant" delta_variable="delta_EGFR" stoichiometry="1" />

```

```

</variable_ref>
<variable_ref variable="EGF_EGFR">
  <role role="product" delta_variable="delta_EGF_EGFR" stoichiometry="1" />
</variable_ref>
<variable_ref variable="r">
  <role role="rate">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply><eq />
        <ci> r </ci>
        <apply><plus />
          <apply><minus />
            <apply><times />
              <ci> k_forward </ci>
              <ci> EGF </ci>
              <ci> EGFR </ci>
            </apply>
          </apply>
        <apply><times />
          <ci> k_reverse </ci>
          <ci> EGF_EGFR </ci>
        </apply>
      </math>
    </role>
  </variable_ref>
</reaction>

```

```
</component>
```

```
<!--
```

```

  This component represents the internalization of the EGF_EGFR
  complex.

```

```
-->
```

```

<component name="EGF_EGFR_internalization" cmeta:id="EGF_EGFR_internalization">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="EGF_EGFR_internalization">
      <dc:title>internalization of the EGF-EGFR complex</dc:title>
    </rdf:Description>
  </rdf:RDF>

```

```

<variable name="EGF_EGFR" public_interface="in" units="concentration_units" />
<variable name="EGF_EGFR_Int" public_interface="in" units="concentration_units" />
<variable name="delta_EGF_EGFR" public_interface="out" units="rate_units" />
<variable name="delta_EGF_EGFR_Int" public_interface="out" units="rate_units" />

```

```
<!--
```

```

  Notice that because variable names need only be unique
  within a component, and not across the entire model, we can
  call the forward and reverse reaction rate constants k_forward
  and k_reverse in this component as well as in the
  EGF_EGFR_bind_rxn component.

```

```
-->
```

```

<variable name="k_forward" initial_value="0.002" units="first_order_rate_constant_units" />
<variable name="k_reverse" initial_value="0.00033" units="second_order_rate_constant_units" />
<variable name="r" units="rate_units" />

```

```
<reaction reversible="yes">
```

```

<variable_ref variable="EGF_EGFR">
  <role role="reactant" delta_variable="delta_EGF_EGFR" stoichiometry="1" />
</variable_ref>
<variable_ref variable="EGF_EGFR_Int">
  <role role="product" delta_variable="delta_EGF_EGFR_Int" stoichiometry="1" />
</variable_ref>
<variable_ref variable="r">
  <role role="rate">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply><eq />
        <ci> r </ci>
        <apply><plus />
          <apply><minus />
            <apply><times />
              <ci> k_forward </ci>
              <ci> EGF_EGFR </ci>
            </apply>
          </apply>
        <apply><times />
          <ci> k_reverse </ci>
          <ci> EGF_EGFR_Int </ci>
        </apply>
      </apply>
    </math>
  </role>
</variable_ref>
</reaction>
</component>

```

```
<!--
```

The *EGF_subsystem* component is a logical component only; i.e., it does not represent any actual chemical species or reaction. It is used to encapsulate the portion of the pathway that results in the EGF-EGFR complex. Note that this is a different use of encapsulation than is shown in the simple two reaction model with encapsulation - instead of encapsulating intermediate reactions, we are encapsulating a complete subsystem. This configuration hides the components representing the EGF and EGFR species. This means that these species cannot be used by any other reaction in the model. If we wanted to make it possible to later add reactions controlling the production of EGF, for instance, we would need to break this encapsulation.

```
-->
```

```

<component name="EGF_subsystem" cmeta:id="EGF_subsystem">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="EGF_subsystem">
      <dc:title>EGF-EGFR subpathway</dc:title>

```

```
<!--
```

The Annotation metadata has associated metadata: the creator and the create date. These pieces of metadata refer to the annotation, not to the model component.

```
-->
```

```

<cmeta:comment rdf:parseType="Resource">
  <rdf:value>

```

The EGF subsystem encompasses the reactions that control the concentration of the activated EGF-EGFR complex.

```

    </rdf:value>
    <dc:creator rdf:parseType="Resource">
      <vCard:N rdf:parseType="Resource">
        <vCard:Family>Nelson</vCard:Family>
        <vCard:Given>Melanie</vCard:Given>
      </vCard:N>
    </dc:creator>
    <dcterms:created rdf:parseType="Resource">
      <dcterms:W3CDTF>2000-11-20</dcterms:W3CDTF>
    </dcterms:created>
  </cmeta:comment>
</rdf:Description>
</rdf:RDF>

<!--
  The subsystem produces the concentration of the EGF-EGFR
  complex as output. This variable has a public interface of
  "out", which means that it can be connected to other components
  in the main pathway. It has a private interface of "in", which
  means that the actual value of the concentration must be passed in
  to this component from one of the components it encapsulates.
-->
<variable name="EGF_EGFR" public_interface="out" private_interface="in" units="concentration" />

<!--
  The subsystem requires time to be passed in from the main
  network, hence the public interface for the time variable is "in".
  The subsystem component then must pass the time variable on
  to the components that it encapsulates, and therefore this
  variable has a private interface of "out".
-->
<variable name="time" public_interface="in" private_interface="out" units="second" />
</component>

<!--
  The group element defines the encapsulation relationship between
  the logical EGF_subsystem component and the components that actually
  make up that subsystem (the EGF, EGFR, EGF_EGFR, and EGF_EGFR_Int
  components)
-->
<group>
  <relationship_ref relationship="encapsulation" />
  <component_ref component="EGF_subsystem">
    <component_ref component="EGF" />
    <component_ref component="EGFR" />
    <component_ref component="EGF_EGFR" />
    <component_ref component="EGF_EGFR_Int" />
    <component_ref component="EGF_EGFR_bind_rxn" />
    <component_ref component="EGF_EGFR_internalization" />
  </component_ref>
</group>

<!--
  The connections hold the actual mappings between variables declared
  in different components. When more than one variable is mapped
  between two components, all variable mappings must be listed in
  the same connection element (there can only be one connection

```

between two components). The modeller should NOT rely on matching the names of the variables in the two components.

-->

```
<connection>
  <map_components component_1="environment" component_2="EGF_subsystem" />
  <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
  <map_components component_1="EGF" component_2="EGF_EGFR_bind_rxn" />
  <map_variables variable_1="EGF" variable_2="EGF" />
  <map_variables variable_1="delta_EGF" variable_2="delta_EGF" />
</connection>

<connection>
  <map_components component_1="EGFR" component_2="EGF_EGFR_bind_rxn" />
  <map_variables variable_1="EGFR" variable_2="EGFR" />
  <map_variables variable_1="delta_EGFR" variable_2="delta_EGFR" />
</connection>

<connection>
  <map_components component_1="EGF_EGFR" component_2="EGF_EGFR_bind_rxn" />
  <map_variables variable_1="EGF_EGFR" variable_2="EGF_EGFR" />
  <map_variables variable_1="delta1_EGF_EGFR" variable_2="delta_EGF_EGFR" />
</connection>

<connection>
  <map_components component_1="EGF_EGFR" component_2="EGF_EGFR_internalization" />
  <map_variables variable_1="EGF_EGFR" variable_2="EGF_EGFR" />
  <map_variables variable_1="delta2_EGF_EGFR" variable_2="delta_EGF_EGFR" />
</connection>

<connection>
  <map_components component_1="EGF_EGFR_Int" component_2="EGF_EGFR_internalization" />
  <map_variables variable_1="EGF_EGFR_Int" variable_2="EGF_EGFR_Int" />
  <map_variables variable_1="delta_EGF_EGFR_Int" variable_2="delta_EGF_EGFR_Int" />
</connection>

<connection>
  <map_components component_1="EGF_subsystem" component_2="EGF" />
  <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
  <map_components component_1="EGF_subsystem" component_2="EGFR" />
  <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
  <map_components component_1="EGF_subsystem" component_2="EGF_EGFR" />
  <map_variables variable_1="time" variable_2="time" />
  <map_variables variable_1="EGF_EGFR" variable_2="EGF_EGFR" />
</connection>

<connection>
  <map_components component_1="EGF_subsystem" component_2="EGF_EGFR_Int" />
  <map_variables variable_1="time" variable_2="time" />
</connection>
```

<!--

The rest of the model is "flat"; i.e., there are no additional encapsulated subsystems.

-->

<component name="SHC" cmeta:id="SHC">

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/

<rdf:Description rdf:about="SHC">

<dc:title>

inactive Src homology 2 domain-containing protein

</dc:title>

<cmeta:bio_entity>

Src homology 2 domain-containing protein

</cmeta:bio_entity>

</rdf:Description>

</rdf:RDF>

<variable name="SHC" public_interface="out" initial_value="0.5" units="concentration_uni

<variable name="delta_SHC" public_interface="in" units="rate_units" />

<variable name="time" public_interface="in" units="second" />

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply><eq />

<apply><diff />

<bvar><ci> time </ci></bvar>

<ci> SHC </ci>

</apply>

<ci> delta_SHC </ci>

</apply>

</math>

</component>

<component name="SHC_active" cmeta:id="SHC_active">

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/

<rdf:Description rdf:about="SHC_active">

<dc:title>

active Src homology 2 domain-containing protein

</dc:title>

<cmeta:bio_entity>

Src homology 2 domain-containing protein

</cmeta:bio_entity>

</rdf:Description>

</rdf:RDF>

<variable name="SHC_active" public_interface="out" initial_value="0.0" units="concentrat

<variable name="delta1_SHC_active" public_interface="in" units="rate_units" />

<variable name="delta2_SHC_active" public_interface="in" units="rate_units" />

<variable name="time" public_interface="in" units="second" />

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply><eq />

<apply><diff />

<bvar><ci> time </ci></bvar>

<ci> SHC_active </ci>

</apply>

<apply><plus />

<ci> delta1_SHC_active </ci>

```

        <ci> delta2_SHC_active </ci>
    </apply>
</apply>
</math>
</component>

<component name="SHC_activation_rxn" cmeta:id="SHC_activation_rxn">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="SHC_activation_rxn">
      <dc:title>activation of SHC</dc:title>
    </rdf:Description>
  </rdf:RDF>

  <variable name="SHC" public_interface="in" units="concentration_units" />
  <variable name="SHC_active" public_interface="in" units="concentration_units" />
  <variable name="delta_SHC" public_interface="out" units="rate_units" />
  <variable name="delta_SHC_active" public_interface="out" units="rate_units" />
  <variable name="EGF_EGFR" public_interface="in" units="concentration_units" />
  <variable name="kcat" initial_value="0.2" units="second" />
  <variable name="km" initial_value="0.833333333" units="concentration_units" />
  <variable name="k1" initial_value="0.0016667" units="first_order_rate_constant_units" />
  <variable name="r" units="rate_units" />
  <!--
  The EGF-EGFR complex is a catalyst in this reaction.
  -->
  <reaction reversible="yes">
    <variable_ref variable="SHC">
      <role role="reactant" delta_variable="delta_SHC" stoichiometry="1" />
    </variable_ref>
    <variable_ref variable="SHC_active">
      <role role="product" delta_variable="delta_SHC_active" stoichiometry="1" />
    </variable_ref>
    <variable_ref variable="EGF_EGFR">
      <role role="catalyst" stoichiometry="1" />
    </variable_ref>
    <variable_ref variable="r">
      <role role="rate">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <apply><eq />
            <ci> r </ci>
            <apply><plus />
              <apply><times />
                <ci> k1 </ci>
                <ci> SHC_active </ci>
              </apply>
            <apply><minus />
              <apply><divide />
                <apply><times />
                  <ci> kcat </ci>
                  <ci> EGF_EGFR </ci>
                  <ci> SHC </ci>
                </apply>
              <apply><plus />
                <ci> km </ci>
                <ci> SHC </ci>
              </apply>
            </apply>
          </math>
        </role>
      </variable_ref>
    </reaction>

```

```

    </apply>
  </apply>
</math>
</role>
</variable_ref>
</reaction>
</component>

```

```

<component name="SOS" cmeta:id="SOS">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="SOS">
      <dc:title>
        inactive son of sevenless
      </dc:title>
      <cmeta:bio_entity>
        son of sevenless
      </cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

```

```

<variable name="SOS" public_interface="out" initial_value="0.1" units="concentration_units" />
<variable name="delta1_SOS" public_interface="in" units="rate_units" />
<variable name="delta2_SOS" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci> time </ci></bvar>
      <ci> SOS </ci>
    </apply>
    <apply><plus />
      <ci> delta1_SOS </ci>
      <ci> delta2_SOS </ci>
    </apply>
  </apply>
</math>
</component>

```

```

<component name="GRB2">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="GRB2">
      <dc:title>
        growth factor receptor bound protein 2
      </dc:title>
      <cmeta:bio_entity>
        growth factor receptor bound protein 2
      </cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

```

```

<variable name="GRB2" public_interface="out" initial_value="1.0" units="concentration_units" />
<variable name="delta1_GRB2" public_interface="in" units="rate_units" />
<variable name="delta2_GRB2" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">

```

```

<apply><eq />
  <apply><diff />
    <bvar><ci>time</ci></bvar>
    <ci>GRB2</ci>
  </apply>
  <apply><plus />
    <ci>delta1_GRB2</ci>
    <ci>delta2_GRB2</ci>
  </apply>
</apply>
</math>
</component>

```

```

<component name="SOS_GRB2">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="SOS_GRB2">
      <dc:title>
        son of sevenless-growth factor receptor bound protein 2 complex
      </dc:title>
      <cmeta:bio_entity>
        complex of son of sevenless and growth factor receptor
        bound protein 2
      </cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

```

```

<variable name="SOS_GRB2" public_interface="out" initial_value="0.0" units="concentration" />
<variable name="delta1_SOS_GRB2" public_interface="in" units="rate_units" />
<variable name="delta2_SOS_GRB2" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci> time </ci></bvar>
      <ci> SOS_GRB2 </ci>
    </apply>
    <apply><plus />
      <ci> delta1_SOS_GRB2 </ci>
      <ci> delta2_SOS_GRB2 </ci>
    </apply>
  </apply>
</math>
</component>

```

```

<component name="SOS_GRB2_binding_rxn">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="SOS_GRB2_binding_rxn">
      <dc:title>SOS-GRB2 binding reaction</dc:title>
    </rdf:Description>
  </rdf:RDF>

```

```

<variable name="SOS" public_interface="in" units="concentration_units" />
<variable name="GRB2" public_interface="in" units="concentration_units" />
<variable name="SOS_GRB2" public_interface="in" units="concentration_units" />
<variable name="delta_SOS" public_interface="out" units="rate_units" />
<variable name="delta1_GRB2" public_interface="out" units="rate_units" />

```

```

<variable name="delta_SOS_GRB2" public_interface="out" units="rate_units" />
<variable name="k1" initial_value="0.000000041667" units="second_order_rate_constant_uni
<variable name="k2" initial_value="0.0168" units="first_order_rate_constant_units" />
<variable name="r" units="rate_units" />

<reaction reversible="yes">
  <variable_ref variable="SOS">
    <role role="reactant" delta_variable="delta_SOS" stoichiometry="1" />
  </variable_ref>
  <variable_ref variable="GRB2">
    <role role="reactant" delta_variable="delta1_GRB2" stoichiometry="1" />
  </variable_ref>
  <variable_ref variable="SOS_GRB2">
    <role role="product" delta_variable="delta_SOS_GRB2" stoichiometry="1" />
  </variable_ref>
  <variable_ref variable="r">
    <role role="rate">
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply><eq />
          <ci> r </ci>
          <apply><plus />
            <apply><minus />
              <apply><times />
                <ci> k1 </ci>
                <ci> SOS </ci>
                <ci> GRB2 </ci>
              </apply>
            </apply>
          <apply><times />
            <ci> k2 </ci>
            <ci> SOS_GRB2 </ci>
          </apply>
        </apply>
      </math>
    </role>
  </variable_ref>
</reaction>
</component>

<component name="SHC_active_SOS_GRB2">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org
  <rdf:Description rdf:about="SHC_active_SOS_GRB2">
    <dc:title>
      complex of activated SHC, SOS, and GRB2
    </dc:title>
    <cmeta:bio_entity>
      complex of activated src homology domain 2 containing protein,
      son of sevenless, and growth factor receptor bound protein 2
    </cmeta:bio_entity>
  </rdf:Description>
</rdf:RDF>

<variable name="SHC_active_SOS_GRB2" public_interface="out" initial_value="1.0" units="c
<variable name="delta_SHC_active_SOS_GRB2" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />

<math xmlns="http://www.w3.org/1998/Math/MathML">

```

```

    <apply><eq />
      <apply><diff />
        <bvar><ci> time </ci></bvar>
        <ci> SHC_active_SOS_GRB2 </ci>
      </apply>
    <ci> delta_SHC_active_SOS_GRB2 </ci>
  </apply>
</math>
</component>

<component name="SHC_active_SOS_GRB2_binding_rxn" cmeta:id="SHC_active_SOS_GRB2_binding_rxn"
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/"
    <rdf:Description rdf:about="SHC_active_SOS_GRB2_binding_rxn">
      <dc:title>
        binding reaction of activated SHC and the SOS-GRB2 complex
      </dc:title>
    </rdf:Description>
  </rdf:RDF>

  <variable name="SHC_active_SOS_GRB2" public_interface="in" units="concentration_units" />
  <variable name="SHC_active" public_interface="in" units="concentration_units" />
  <variable name="SOS_GRB2" public_interface="in" units="concentration_units" />
  <variable name="delta_SHC_active" public_interface="out" units="rate_units" />
  <variable name="delta_SOS_GRB2" public_interface="out" units="rate_units" />
  <variable name="delta_SHC_active_SOS_GRB2" public_interface="out" units="rate_units" />
  <variable name="k1" initial_value="0.000000833" units="second_order_rate_constant_units" />
  <variable name="k2" initial_value="0.1" units="first_order_rate_constant_units" />
  <variable name="r" units="rate_units" />

  <reaction reversible="yes">
    <variable_ref variable="SHC_active">
      <role role="reactant" delta_variable="delta_SHC_active" stoichiometry="1" />
    </variable_ref>
    <variable_ref variable="SOS_GRB2">
      <role role="reactant" delta_variable="delta_SOS_GRB2" stoichiometry="1" />
    </variable_ref>
    <variable_ref variable="SHC_active_SOS_GRB2">
      <role role="product" delta_variable="delta_SHC_active_SOS_GRB2" stoichiometry="1" />
    </variable_ref>
    <variable_ref variable="r">
      <role role="rate">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
          <apply><eq />
            <ci> r </ci>
            <apply><plus />
              <apply><minus />
                <apply><times />
                  <ci> k1 </ci>
                  <ci> SHC_active </ci>
                  <ci> SOS_GRB2 </ci>
                </apply>
              </apply>
            <apply><times />
              <ci> k2 </ci>
              <ci> SHC_active_SOS_GRB2 </ci>
            </apply>
          </math>
        </role>
      </variable_ref>
    </reaction>

```

```
    </math>
  </role>
</variable_ref>
</reaction>
</component>
```

```
<component name="GDP_ras" cmeta:id="GDP_ras">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="GDP_ras">
      <!--
        This component has two alternative names, which is indicated by
        simply repeating the title metadata element.
      -->
      <dc:title>inactive Ras</dc:title>
      <dc:title>GDP-bound Ras</dc:title>
      <cmeta:bio_entity>Ras</cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>
```

```
<variable name="GDP_ras" public_interface="out" initial_value="0.0" units="concentration" />
<variable name="delta_GDP_ras" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />
```

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci> time </ci></bvar>
      <ci> GDP_ras </ci>
    </apply>
    <ci> delta_GDP_ras </ci>
  </apply>
</math>
</component>
```

```
<component name="GTP_ras" cmeta:id="GTP_ras">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="GTP_ras">
      <dc:title>active Ras</dc:title>
      <dc:title>GTP-bound Ras</dc:title>
      <cmeta:bio_entity>Ras</cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>
```

```
<variable name="GTP_ras" public_interface="out" initial_value="0.0" units="concentration" />
<variable name="delta_GTP_ras" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />
```

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci> time </ci></bvar>
      <ci> GTP_ras </ci>
    </apply>
    <ci> delta_GTP_ras </ci>
  </apply>
</math>
</component>
```

```

<component name="Ras_activation_rxn" cmeta:id="Ras_activation_rxn">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/
  <rdf:Description rdf:about="Ras_activation_rxn">
    <dc:title>activation of Ras</dc:title>
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Ras is activated when GDP dissociates, and GTP binds
      </rdf:value>
      <dc:creator rdf:parseType="Resource">
        <vCard:N rdf:parseType="Resource">
          <vCard:Family>Nelson</vCard:Family>
          <vCard:Given>Melanie</vCard:Given>
        </vCard:N>
      </dc:creator>
      <dcterms:created>
        <dcterms:W3CDTF>2000-11-20</dcterms:W3CDTF>
      </dcterms:created>
    </cmeta:comment>

    <!--
      It is perfectly legal to add a second annotation. In fact,
      it is best to try to break annotations into "single data units",
      i.e., have each annotation only discuss one topic. This will
      make it easier to perform structured searches on the metadata.
    -->
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        The Ras activation reaction is modeled as irreversible
      </rdf:value>
      <dc:creator rdf:parseType="Resource">
        <vCard:N rdf:parseType="Resource">
          <vCard:Family>Nelson</vCard:Family>
          <vCard:Given>Melanie</vCard:Given>
        </vCard:N>
      </dc:creator>
      <dcterms:created>
        <dcterms:W3CDTF>2000-11-21</dcterms:W3CDTF>
      </dcterms:created>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

<variable name="GDP_ras" public_interface="in" units="concentration_units" />
<variable name="GTP_ras" public_interface="in" units="concentration_units" />
<variable name="delta_GDP_ras" public_interface="out" units="rate_units" />
<variable name="delta_GTP_ras" public_interface="out" units="rate_units" />
<variable name="SHC_active_SOS_GRB2" public_interface="in" units="concentration_units" />
<variable name="kcat" initial_value="0.02" units="first_order_rate_constant_units" />
<variable name="km" initial_value="0.50505" units="concentration_units" />
<variable name="r" units="rate_units" />

<reaction reversible="no">
  <variable_ref variable="GDP_ras">
    <role role="reactant" delta_variable="delta_GDP_ras" stoichiometry="1" />
  </variable_ref>
  <variable_ref variable="GTP_ras">
    <role role="product" delta_variable="delta_GTP_ras" stoichiometry="1" />
  </variable_ref>

```

```

</variable_ref>
<variable_ref variable="SHC_active_SOS_GRB2">
  <role role="catalyst" />
</variable_ref>
<variable_ref variable="r">
  <role role="rate">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply><eq />
        <ci> r </ci>
        <apply><minus />
          <apply><divide />
            <apply><times />
              <ci> kcat</ci>
              <ci> SHC_active_SOS_GRB2 </ci>
              <ci> GDP_ras </ci>
            </apply>
          <apply><plus />
            <ci> km</ci>
            <ci> GDP_ras </ci>
          </apply>
        </apply>
      </math>
    </role>
  </variable_ref>
</reaction>
</component>

```

```

<component name="SOS_active" cmeta:id="SOS_active">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="SOS_active">
      <dc:title>
        active son of sevenless
      </dc:title>
      <cmeta:bio_entity>
        son of sevenless
      </cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

```

```

<variable name="SOS_active" public_interface="out" initial_value="0.0" units="concentration" />
<variable name="delta1_SOS_active" public_interface="in" units="rate_units" />
<variable name="delta2_SOS_active" public_interface="in" units="rate_units" />
<variable name="time" public_interface="in" units="second" />

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci> time </ci></bvar>
      <ci> SOS_active </ci>
    </apply>
    <apply><plus />
      <ci> delta1_SOS_active </ci>
      <ci> delta2_SOS_active </ci>
    </apply>
  </math>

```

```
</component>
```

```
<!--
```

```
The MAPK_active component only participates in this pathway as an
activator. Its concentration remains constant (or may perhaps be a
parameter that the modeller adjusts in exploring the behaviour of this
pathway). Therefore there are no mathematics in this component. In a more
complex example, this component might be another encapsulated subsystem,
representing the signal transduction pathway that leads to the
production of activated MAPK. Creating a component to represent MAPK
(rather than simply including a variable to represent the concentration
of MAPK in the relevant reaction component) makes it easier to add more
detail to the model later.
```

```
-->
```

```
<component name="MAPK_active" cmeta:id="MAPK_active">
```

```
<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org
```

```
<rdf:Description rdf:about="MAPK_active">
```

```
<dc:title>active MAP kinase</dc:title>
```

```
<cmeta:bio_entity>MAP kinase</cmeta:bio_entity>
```

```
</rdf:Description>
```

```
</rdf:RDF>
```

```
<variable name="MAPK_active" public_interface="out" initial_value="1.0" units="concentrat
```

```
</component>
```

```
<component name="SOS_activation_rxn" cmeta:id="SOS_activation_rxn">
```

```
<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org
```

```
<rdf:Description rdf:about="SOS_activation_rxn">
```

```
<dc:title>activation of SOS</dc:title>
```

```
</rdf:Description>
```

```
</rdf:RDF>
```

```
<variable name="SOS" public_interface="in" units="concentration_units" />
```

```
<variable name="SOS_active" public_interface="in" units="concentration_units" />
```

```
<variable name="MAPK_active" public_interface="in" units="concentration_units" />
```

```
<variable name="delta_SOS" public_interface="out" units="rate_units" />
```

```
<variable name="delta_SOS_active" public_interface="out" units="rate_units" />
```

```
<variable name="kcat" initial_value="10.0" units="first_order_rate_constant_units" />
```

```
<variable name="km" initial_value="2.564167" units="concentration_units" />
```

```
<variable name="k1" initial_value="0.001" units="first_order_rate_constant_units" />
```

```
<variable name="r" units="rate_units" />
```

```
<reaction reversible="yes">
```

```
<variable_ref variable="SOS">
```

```
<role role="reactant" delta_variable="delta_SOS" stoichiometry="1" />
```

```
</variable_ref>
```

```
<variable_ref variable="SOS_active">
```

```
<role role="product" delta_variable="delta_SOS_active" stoichiometry="1" />
```

```
</variable_ref>
```

```
<variable_ref variable="MAPK_active">
```

```
<role role="catalyst" />
```

```
</variable_ref>
```

```
<variable_ref variable="r">
```

```
<role role="rate">
```

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
```

```
<apply><eq />
```

```
<ci> r </ci>
```

```

    <apply><minus />
      <apply><times />
        <ci> k1 </ci>
        <ci> SOS_active </ci>
      </apply>
    <apply><divide />
      <apply><times />
        <ci> kcat </ci>
        <ci> MAPK_active </ci>
        <ci> SOS </ci>
      </apply>
    <apply><plus />
      <ci> km </ci>
      <ci> SOS </ci>
    </apply>
  </apply>
</math>
</role>
</variable_ref>
</reaction>
</component>

<component name="SOS_active_GRB2" cmeta:id="SOS_active_GRB2">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="SOS_active_GRB2">
      <dc:title>active SOS-GRB2 complex</dc:title>
      <cmeta:bio_entity>complex of active SOS and GRB2</cmeta:bio_entity>
    </rdf:Description>
  </rdf:RDF>

  <variable name="SOS_active_GRB2" public_interface="out" initial_value="0.0" units="concentration_units" />
  <variable name="delta_SOS_active_GRB2" public_interface="in" units="rate_units" />
  <variable name="time" public_interface="in" units="second" />

  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply><eq />
      <apply><diff />
        <bvar><ci> time </ci></bvar>
        <ci> SOS_active_GRB2 </ci>
      </apply>
      <ci> delta_SOS_active_GRB2 </ci>
    </apply>
  </math>
</component>

<component name="SOS_active_GRB2_binding_rxn" cmeta:id="SOS_active_GRB2_binding_rxn">
  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:dc="http://purl.org/dc/terms/">
    <rdf:Description rdf:about="SOS_active_GRB2_binding_rxn">
      <dc:title>binding reaction of activated SOS and GRB2</dc:title>
    </rdf:Description>
  </rdf:RDF>

  <variable name="SOS_active" public_interface="in" units="concentration_units" />
  <variable name="SOS_active_GRB2" public_interface="in" units="concentration_units" />
  <variable name="GRB2" public_interface="in" units="concentration_units" />

```

```

<variable name="delta_SOS_active" public_interface="out" units="rate_units" />
<variable name="delta2_GRB2" public_interface="out" units="rate_units" />
<variable name="delta_SOS_active_GRB2" public_interface="out" units="rate_units" />
<variable name="k1" initial_value="0.000000041667" units="second_order_rate_constant_units" />
<variable name="k2" initial_value="0.0168" units="first_order_rate_constant_units" />
<variable name="r" units="rate_units" />

<reaction reversible="yes">
  <variable_ref variable="SOS_active">
    <role role="reactant" delta_variable="delta_SOS_active" stoichiometry="1" />
  </variable_ref>
  <variable_ref variable="GRB2">
    <role role="reactant" delta_variable="delta2_GRB2" stoichiometry="1" />
  </variable_ref>
  <variable_ref variable="SOS_active_GRB2">
    <role role="product" delta_variable="delta_SOS_active_GRB2" stoichiometry="1" />
  </variable_ref>
  <variable_ref variable="r">
    <role role="rate">
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply><eq />
          <ci> r </ci>
          <apply><plus />
            <apply><minus />
              <apply><times />
                <ci> k1 </ci>
                <ci> SOS_active </ci>
                <ci> GRB2 </ci>
              </apply>
            </apply>
          <apply><times />
            <ci> k2 </ci>
            <ci> SOS_active_GRB2 </ci>
          </apply>
        </math>
      </role>
    </variable_ref>
  </reaction>
</component>

<!--
  The following connections distribute the variable "time" to all of the
  species components.
-->
<connection>
  <map_components component_1="environment" component_2="SHC" />
  <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
  <map_components component_1="environment" component_2="SHC_active" />
  <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
  <map_components component_1="environment" component_2="SOS" />

```

```

    <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
    <map_components component_1="environment" component_2="GRB2" />
    <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
    <map_components component_1="environment" component_2="SOS_GRB2" />
    <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
    <map_components component_1="environment" component_2="SHC_active_SOS_GRB2" />
    <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
    <map_components component_1="environment" component_2="GDP_ras" />
    <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
    <map_components component_1="environment" component_2="GTP_ras" />
    <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
    <map_components component_1="environment" component_2="SOS_active" />
    <map_variables variable_1="time" variable_2="time" />
</connection>

<connection>
    <map_components component_1="environment" component_2="SOS_active_GRB2" />
    <map_variables variable_1="time" variable_2="time" />
</connection>

<!-- Connections for the SHC activation reaction. -->
<connection>
    <map_components component_1="SHC" component_2="SHC_activation_rxn" />
    <map_variables variable_1="SHC" variable_2="SHC" />
    <map_variables variable_1="delta_SHC" variable_2="delta_SHC" />
</connection>

<connection>
    <map_components component_1="SHC_active" component_2="SHC_activation_rxn" />
    <map_variables variable_1="SHC_active" variable_2="SHC_active" />
    <map_variables variable_1="delta1_SHC_active" variable_2="delta_SHC_active" />
</connection>

<!--
This connection is to the component that encapsulates the entire EGF
subsystem. Notice that as long as the interface presented by this
encapsulating component remains the same (in this case, the interface
consists solely of the concentration of the EGF-EGFR complex), the
inner workings of that subsystem can be changed without affecting
the rest of the model at all.
-->

```

```

<connection>
  <map_components component_1="SHC_activation_rxn" component_2="EGF_subsystem" />
  <map_variables variable_1="EGF_EGFR" variable_2="EGF_EGFR" />
</connection>

<!-- Connections for the SHC_active - SOS_GRB2 binding reaction. -->
<connection>
  <map_components component_1="SHC_active" component_2="SHC_active_SOS_GRB2_binding_rxn" />
  <map_variables variable_1="SHC_active" variable_2="SHC_active" />
  <map_variables variable_1="delta2_SHC_active" variable_2="delta_SHC_active" />
</connection>

<connection>
  <map_components component_1="SOS_GRB2" component_2="SHC_active_SOS_GRB2_binding_rxn" />
  <map_variables variable_1="SOS_GRB2" variable_2="SOS_GRB2" />
  <map_variables variable_1="delta2_SOS_GRB2" variable_2="delta_SOS_GRB2" />
</connection>

<connection>
  <map_components component_1="SHC_active_SOS_GRB2" component_2="SHC_active_SOS_GRB2_binding_rxn" />
  <map_variables variable_1="SHC_active_SOS_GRB2" variable_2="SHC_active_SOS_GRB2" />
  <map_variables variable_1="delta_SHC_active_SOS_GRB2" variable_2="delta_SHC_active_SOS_GRB2" />
</connection>

<!-- Connections for the SOS - GRB2 binding reaction. -->
<connection>
  <map_components component_1="SOS" component_2="SOS_GRB2_binding_rxn" />
  <map_variables variable_1="SOS" variable_2="SOS" />
  <map_variables variable_1="delta1_SOS" variable_2="delta_SOS" />
</connection>

<connection>
  <map_components component_1="GRB2" component_2="SOS_GRB2_binding_rxn" />
  <map_variables variable_1="GRB2" variable_2="GRB2" />
  <map_variables variable_1="delta1_GRB2" variable_2="delta1_GRB2" />
</connection>

<connection>
  <map_components component_1="SOS_GRB2" component_2="SOS_GRB2_binding_rxn" />
  <map_variables variable_1="SOS_GRB2" variable_2="SOS_GRB2" />
  <map_variables variable_1="delta1_SOS_GRB2" variable_2="delta_SOS_GRB2" />
</connection>

<!-- connections for the SOS activation reaction -->
<connection>
  <map_components component_1="SOS" component_2="SOS_activation_rxn" />
  <map_variables variable_1="SOS" variable_2="SOS" />
  <map_variables variable_1="delta2_SOS" variable_2="delta_SOS" />
</connection>

<connection>
  <map_components component_1="SOS_active" component_2="SOS_activation_rxn" />
  <map_variables variable_1="SOS_active" variable_2="SOS_active" />
  <map_variables variable_1="delta1_SOS_active" variable_2="delta_SOS_active" />
</connection>

<connection>
  <map_components component_1="MAPK_active" component_2="SOS_activation_rxn" />
  <map_variables variable_1="MAPK_active" variable_2="MAPK_active" />

```

```

</connection>

<!-- Connections for the SOS_active - GRB2 binding reaction. -->
<connection>
  <map_components component_1="SOS_active" component_2="SOS_active_GRB2_binding_rxn" />
  <map_variables variable_1="SOS_active" variable_2="SOS_active" />
  <map_variables variable_1="delta2_SOS_active" variable_2="delta_SOS_active" />
</connection>

<connection>
  <map_components component_1="GRB2" component_2="SOS_active_GRB2_binding_rxn" />
  <map_variables variable_1="GRB2" variable_2="GRB2" />
  <map_variables variable_1="delta2_GRB2" variable_2="delta2_GRB2" />
</connection>

<connection>
  <map_components component_1="SOS_active_GRB2" component_2="SOS_active_GRB2_binding_rxn" />
  <map_variables variable_1="SOS_active_GRB2" variable_2="SOS_active_GRB2" />
  <map_variables variable_1="delta_SOS_active_GRB2" variable_2="delta_SOS_active_GRB2" />
</connection>

<!-- Connections for the Ras activation reaction. -->
<connection>
  <map_components component_1="GDP_ras" component_2="Ras_activation_rxn" />
  <map_variables variable_1="GDP_ras" variable_2="GDP_ras" />
  <map_variables variable_1="delta_GDP_ras" variable_2="delta_GDP_ras" />
</connection>

<connection>
  <map_components component_1="GTP_ras" component_2="Ras_activation_rxn" />
  <map_variables variable_1="GTP_ras" variable_2="GTP_ras" />
  <map_variables variable_1="delta_GTP_ras" variable_2="delta_GTP_ras" />
</connection>

<connection>
  <map_components component_1="SHC_active_SOS_GRB2" component_2="Ras_activation_rxn" />
  <map_variables variable_1="SHC_active_SOS_GRB2" variable_2="SHC_active_SOS_GRB2" />
</connection>

</model>

```