

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

```
<!-- FILE : smith_crampin_Na_K_pump_2004.xml
```

```
CREATED : 26th April 2004
```

```
LAST MODIFIED : 26th April 2004
```

```
AUTHOR : Alice Boit  
         Bioengineering Institute  
         The University of Auckland
```

```
MODEL STATUS : This model conforms to the CellML 1.0 Specification released on  
10th August 2001, and the 16/01/2002 CellML Metadata 1.0 Specification.
```

```
DESCRIPTION : This file contains a CellML description of N. P. Smith' and E. Crampin's 2004 m
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```
CHANGES:
```

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```

```
<model name="smith_crampin_Na_K_pump_2004" cmeta:id="smith_crampin_Na_K_pump_2004" xmlns="ht
```

```
<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#" xmlns:bgs="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 Model Builder Metadata. The Dublin Core "creator" element is used  
to indicate the person who translated the model into CellML.
```

```
-->
```

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

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

```
<vCard:Family>Boit</vCard:Family>
```

```
<vCard:Given>Alice</vCard:Given>
```

```
</vCard:N>
```

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

```
<rdf:value>a.boit@auckland.ac.nz</rdf:value>
```

```
<rdf:type rdf:resource="http://imc.org/vCard/3.0#internet" />
```

```
</vCard:EMAIL>
```

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

```
<vCard:Orgname>The University of Auckland</vCard:Orgname>
```

```
<vCard:Orgunit>The Bioengineering Institute</vCard:Orgunit>
```

```
</vCard:ORG>
```

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

```
<!--
```

```
The Creation Date metadata. This is the date on which the model  
was translated into CellML.
```

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-->
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```
<dcterms:created rdf:parseType="Resource">
```

```
<dcterms:W3CDTF>2004-04-26</dcterms:W3CDTF>
```

```
</dcterms:created>
```

```

<!-- The Publisher metadata. -->
<dc:publisher>
  The University of Auckland, Bioengineering Institute
</dc:publisher>
</rdf:Description>

<!--
  The following metadata refers to the model itself, as indicated by the
  reference to the ID "smith_crampin_Na_K_pump_2004", which is declared on the
  <model> element.
-->

<rdf:Description rdf:about="#smith_crampin_Na_K_pump_2004">
  <!-- A human readable name for the model. -->
  <dc:title>
    N. P. Smith' and E. Crampin's 2004 mathematical model of the cardiac sodium-potassium
  </dc:title>

  <!-- A comment regarding the model. -->
  <cmeta:comment rdf:parseType="Resource">
    <rdf:value>
      This is the CellML description of N. P. Smith' and E. Crampin's 2004
      mathematical model of the cardiac sodium-potassium pump.
    </rdf:value>
    <!-- The creator of the comment. -->
    <dc:creator rdf:parseType="Resource">
      <vCard:FN>Alice Boit</vCard:FN>
    </dc:creator>
  </cmeta:comment>

  <cmeta:bio_entity>Cardiac Myocyte</cmeta:bio_entity>

  <!-- Keyword(s) -->
  <bqs:reference rdf:parseType="Resource">
    <dc:subject rdf:parseType="Resource">
      <bqs:subject_type>keyword</bqs:subject_type>
      <rdf:value>
        <rdf:Bag>
          <rdf:li>Cardiac Myocyte</rdf:li>
          <rdf:li>Cardiac Electrophysiology</rdf:li>
          <rdf:li>electrophysiology</rdf:li>
        </rdf:Bag>
      </rdf:value>
    </dc:subject>
  </bqs:reference>

  <!--
  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
  such as Pubmed. All associated data such as author, journal title,
  date, etc can be looked up on the database.
-->

  <bqs:reference rdf:parseType="Resource">
    <!--In Press at the time the model was coded. Will be added later-->
    <bqs:Pubmed_id> </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>Smith</vCard:Family>
        <vCard:Given>N</vCard:Given>
        <vCard:Other>P</vCard:Other>
      </vCard:N>
    </bqs:Person>
  </rdf:li>

  <rdf:li rdf:parseType="Resource">
    <bqs:Person rdf:parseType="Resource">
      <vCard:N rdf:parseType="Resource">
        <vCard:Family>Crampin</vCard:Family>
        <vCard:Given>E</vCard:Given>
        <vCard:Given>J</vCard:Given>
      </vCard:N>
    </bqs:Person>
  </rdf:li>

</rdf:Seq>
</dc:creator>
<dc:title>
Development of models of active ion transport for whole-cell modelling: cardiac so
</dc:title>
<!--In Press at the time the model was coded. Will be added later-->
<dcterms:issued rdf:parseType="Resource">
  <dcterms:W3CDTF>2004</dcterms:W3CDTF>
</dcterms:issued>
<bqs:Journal rdf:parseType="Resource">
  <dc:title>Progress in Biophysics & Molecular Biology</dc:title>
</bqs:Journal>
<bqs:volume />
<bqs:first_page />
<bqs:last_page />
</bqs:JournalArticle>
</bqs:reference>
</rdf:Description>
</rdf:RDF>

```

```

<units name="ms">
  <unit prefix="milli" units="second" />
</units>
<units name="mV">
  <unit prefix="milli" units="volt" />
</units>
<units name="mV_per_ms">
  <unit units="mV" />
  <unit units="ms" exponent="-1" />
</units>
<units name="mM">
  <unit prefix="nano" units="mole" />
  <unit prefix="milli" units="metre" exponent="-3" />
</units>
<units name="mM_per_ms">
  <unit units="mM" />
  <unit units="ms" exponent="-1" />

```

```

</units>
<units name="uA">
  <unit prefix="micro" units="ampere" />
</units>

<!-- Global units used in the NaK_pump-->

<units name="concentration">
  <unit prefix="milli" units="mole" />
  <unit units="litre" exponent="-3" />
</units>
<units name="energy">
  <unit units="joule" />
  <unit units="mole" exponent="-1" />
</units>
<units name="gas_constant">
  <unit units="joule" />
  <unit units="mole" exponent="-1" />
  <unit units="kelvin" exponent="-1" />
</units>
<units name="faraday_constant">
  <unit units="coulomb" />
  <unit units="mole" exponent="-1" />
</units>
<units name="rate">
  <unit units="second" exponent="-1" />
</units>
<units name="minus_k1_rate">
  <unit units="second" exponent="-1" />
  <unit units="mM" exponent="-1" />
</units>
<units name="minus_k3_rate">
  <unit units="second" exponent="-1" />
  <unit units="mM" exponent="-2" />
</units>
<units name="rate_diagram_sum">
  <unit units="second" exponent="-3" />
</units>

<!-- interface component -->

<component name="interface">

  <!-- Variables we expect to be set/controlled externally -->
  <variable name="t" private_interface="out" units="ms" />
  <variable name="Vm" private_interface="out" initial_value="-150" units="mV" />

  <!-- Variables used in the NaK_pump we expect to be set/controlled externally -->

  <variable name="cMgADP" private_interface="out" initial_value="0.01" units="concentration" />
  <variable name="cNa_i" private_interface="out" initial_value="50." units="concentration" />

  <!-- Variables used in the NaK_pump we want to make available externally and which are computed -->

```

```

<!-- Cycle rate of Na/K-pump -->
  <variable name="v_cyc" public_interface="out" private_interface="in" units="rate" />

<!-- Net Free Energy of cycle -->
  <variable name="net_free_energy" public_interface="out" private_interface="in" units="energy" />

<!-- Some dummy ODEs as a means to handle the three input variables
      (membrane potential, ADP concentration, cytosolic sodium concentration)-->

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci>t</ci></bvar>
      <ci>Vm</ci>
    </apply>
    <cn cellml:units="mV_per_ms">1.0</cn>
  </apply>
</math>
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci>t</ci></bvar>
      <ci>cMgADP</ci>
    </apply>
    <cn cellml:units="concentration">0.0</cn>
  </apply>
</math>
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply><eq />
    <apply><diff />
      <bvar><ci>t</ci></bvar>
      <ci>cNa_i</ci>
    </apply>
    <cn cellml:units="concentration">0.0</cn>
  </apply>
</math>

</component> <!--EO interface-->

<component name="NaK_pump">

  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#NaK_pump">
      <cmeta:comment rdf:parseType="Resource">
        <rdf:value>
          The Na/K-pump is an energy-consuming transporter channel within the membrane.
          It is indispensable for maintaining the electrochemical gradients of the involved
          across the membrane which result in resting Vm. The pump splits up one ATP molecule
          conformational change transporting 3Na outwards and 2K inwards in each cycle.
        </rdf:value>
      </cmeta:comment>
    </rdf:Description>
  </rdf:RDF>

```

```

<!-- Variables and Parameters -->

<!-- Body temperature -->
  <variable name="body_temp" private_interface="out" initial_value="310." units="kelvin" />

<!-- General constants -->
  <variable name="gas_const" private_interface="out" initial_value="8.314" units="gas_constar
  <variable name="faraday_const" private_interface="out" initial_value="96485." units="farada

<!-- Foward and backward rate constants of the reduced 4-state cycle. They are named with 'k

  <variable name="k1" initial_value="1050." units="rate" />
  <variable name="minus_k1" initial_value="172.1" units="minus_k1_rate" />
  <variable name="k2" initial_value="481." units="rate" />
  <variable name="minus_k2" initial_value="40.1" units="rate" />
  <variable name="k3" initial_value="2000." units="rate" />
  <variable name="minus_k3" initial_value="79287.1" units="minus_k3_rate" />
  <variable name="k4" initial_value="320." units="rate" />
  <variable name="minus_k4" initial_value="40.1" units="rate" />

<!-- Kinetic parameters (e: extracellular, i: intracellular). They represent the ratio of con
Note:
the Na-equilibrium constants are set to a
baseline level here because they are functions of Vm, see implementation below. -->

  <variable name="eq_Na_base_e" initial_value="15.5" units="concentration" />
  <variable name="eq_Na_base_i" initial_value="2.49" units="concentration" />
  <variable name="eq_K_e" initial_value="0.213" units="concentration" />
  <variable name="eq_K_i" initial_value="0.5" units="concentration" />
  <variable name="eq_MgATP" initial_value="2.51" units="concentration" />
  <variable name="eq_HPi" initial_value="0.000169" units="concentration" />
  <variable name="eq_KPi" initial_value="292." units="concentration" />
  <variable name="eq_NaPi" initial_value="224." units="concentration" />

<!-- To arrange the calculations for the final transition rates more clearly, we introduc
another parameter set which consists of the ratios between each ion concentration and its
corresponding equilibrium constant. These ratios are dimensionless because we assigned
concentration units to the equilibrium constants.-->

  <variable name="dimless_Na_e" initial_value="0." units="dimensionless" />
  <variable name="dimless_Na_i" initial_value="0." units="dimensionless" />
  <variable name="dimless_K_e" initial_value="0." units="dimensionless" />
  <variable name="dimless_K_i" initial_value="0." units="dimensionless" />
  <variable name="dimless_MgATP" initial_value="0." units="dimensionless" />

<!-- Apparent transition rates of the lumped scheme. These 'alpha's are the actual rate c
in the calculation of the cycle rate v_cyc.
Computing the 'alpha's most times involves the rate constants named with 'k's and the d
calculated before, so that the outcome is in usual reaction rate units of [1/s]. -->
  <variable name="alpha1" initial_value="1.0" units="rate" />
  <variable name="alpha2" initial_value="1.0" units="rate" />
  <variable name="alpha3" initial_value="1.0" units="rate" />
  <variable name="alpha4" initial_value="1.0" units="rate" />

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<variable name="minus_alpha1" initial_value="1.0" units="rate" />
<variable name="minus_alpha2" initial_value="1.0" units="rate" />
<variable name="minus_alpha3" initial_value="1.0" units="rate" />
<variable name="minus_alpha4" initial_value="1.0" units="rate" />

<!-- Molecular concentrations -->
<variable name="cNa_e" initial_value="150." units="concentration" />
<variable name="cK_e" initial_value="5.4" units="concentration" />
<variable name="cK_i" initial_value="140." units="concentration" />
<variable name="cMgATP" initial_value="9.8" units="concentration" />
<variable name="cPi_sum" initial_value="4.2" units="concentration" />
<variable name="cPi" initial_value="0." units="concentration" />
<variable name="cH" initial_value="0.000081283" units="concentration" />

<!-- Energy required to run the pump per cycle consists of two terms; the Na and K contri
<variable name="dG_Na" units="energy" />
<variable name="dG_K" units="energy" />
<variable name="dG_pump" units="energy" />

<!-- Free Energy of ATP hydrolysis -->
<variable name="dG_ATP" units="energy" />

<!-- Partition factor that determines how the voltage dependency of the two Na equilibrium co
<variable name="partition_factor" initial_value="-0.031288692380984445" units="dimensionless" />

<!-- Diagram sum of the four states for the denominator used in calculation of cycle rate v_c
<variable name="diagram_sum" initial_value="0.0" units="rate_diagram_sum" />

<!-- Inputs -->

<!-- Externally set variables: Vm, cMgADP and cNa_i should be regulated via the interface -->
<variable name="Vm" public_interface="in" private_interface="out" units="mV" />
<variable name="cMgADP" public_interface="in" private_interface="out" units="concentration" />
<variable name="cNa_i" public_interface="in" private_interface="out" units="concentration" />

<!-- Outputs computed here -->

<!-- Clockwise cycle rate-->
<variable name="v_cyc" public_interface="out" units="rate" />

<!-- Net Free Energy of cycle -->
<variable name="net_free_energy" public_interface="out" units="energy" />

<!-- compute the concentration of free inorganic phosphate-->

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
  <rdf:Description rdf:about="#cPi">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the concentration of free inorganic phosphate cPi
        related to the total measurable concentration given by cPi_sum.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="cPi"><eq />
    <ci>cPi</ci>
    <apply><divide />
      <ci>cPi_sum</ci>

      <apply><plus />
        <cn cellml:units="dimensionless">1.0</cn>
        <apply><divide />
          <ci>cK_i</ci>
          <ci>eq_KPi</ci>
        </apply>
        <apply><divide />
          <ci>cH</ci>
          <ci>eq_HPi</ci>
        </apply>
        <apply><divide />
          <ci>cNa_i</ci>
          <ci>eq_NaPi</ci>
        </apply>
      </apply>
    </apply>
  </math>

```

*<!-- compute energy required to run pump in dependence of Vm (a positive term). First, the Na*

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#dG_Na_calc_eq">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the Na contribution to dG_pump.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dG_Na_calc"><eq />
    <ci>dG_Na</ci>
    <apply><minus />
      <apply><times />
        <ci>gas_const</ci>
        <ci>body_temp</ci>
        <apply><ln />
          <apply><divide />
            <ci>cNa_e</ci>
            <ci>cNa_i</ci>
          </apply>
        </apply>
      </apply>
    <apply><times />
      <ci>faraday_const</ci>

```

```

        <cn cellml:units="dimensionless">0.001</cn>
        <ci>Vm</ci>
      </apply>
    </apply>
  </apply>
</math>

```

```
<!--K-contribution-->
```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
  <rdf:Description rdf:about="#dG_K_calc_eq">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the K contribution to dG_pump.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dG_K_calc"><eq />
    <ci>dG_K</ci>
    <apply><plus />
      <apply><times />
        <ci>gas_const</ci>
        <ci>body_temp</ci>
      <apply><ln />
        <apply><divide />
          <ci>cK_i</ci>
          <ci>cK_e</ci>
        </apply>
      </apply>
    </apply>
    <apply><times />
      <ci>faraday_const</ci>
      <cn cellml:units="dimensionless">0.001</cn>
      <ci>Vm</ci>
    </apply>
  </apply>
</math>

```

```
<!-- compute energy required to run pump by adding the two contributions-->
```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
  <rdf:Description rdf:about="#dG_pump_calc_eq">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of dG_pump.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

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

```

```

    <ci>dG_pump</ci>
    <apply><plus />
    <apply><times />
    <cn cellml:units="dimensionless">2.0</cn>
  <ci>dG_K</ci>
  </apply>
  <apply><times />
  <cn cellml:units="dimensionless">3.0</cn>
  <ci>dG_Na</ci>
  </apply>
</apply>
</math>

```

*<!-- compute energy released by exergonic hydrolysis of ATP (a negative term).-->*

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
  <rdf:Description rdf:about="#dG_ATP_calc">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation the energy released by ATP hydrolysis.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dG_ATP_calc"><eq />
    <ci>dG_ATP</ci>

    <apply><minus />
    <cn cellml:units="energy">-29600.</cn>
    <apply><times />
  <ci>gas_const</ci>
  <ci>body_temp</ci>
  <apply><ln />
  <apply><divide />
  <ci>cMgATP</ci>
  <apply><times />
  <cn cellml:units="dimensionless">0.001</cn>
  <ci>cMgADP</ci>
  <ci>cPi</ci>
  </apply>
  </apply>
  </apply>
  </apply>
  </apply>
</math>

```

*<!-- compute net free energy by summing up the last two energy terms-->*

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
  <rdf:Description rdf:about="#dG_ATP_calc">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation the net free energy of the cycle.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

    </rdf:value>
  </cmeta:comment>
</rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="net_free_energy_calc"><eq />
    <ci>net_free_energy</ci>
    <apply><plus />
  <ci>dG_ATP</ci>
    <ci>dG_pump</ci>
    </apply>
  </apply>
</math>

```

```

<!-- compute pump cycle rate in dependence of the rate constants. First, calculate the dimens
parameters which represent ratios between each ion concentration and its
corresponding equilibrium constant. Then use these parameters to define the rate constants
lumped scheme (the 'alpha's)-->

```

```

<!-- calculate dimless_Na_i -->

```

```

  <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
    <rdf:Description rdf:about="#dimless_Na_i">
      <cmeta:comment rdf:parseType="Resource">
        <rdf:value>
          Calculation of the dimless_Na_i parameter which is a function of Vm because the e
          dependent on Vm (which occurs in the denominator's exponential).
        </rdf:value>
      </cmeta:comment>
    </rdf:Description>
  </rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dimless_Na_i_calc"><eq />
    <ci>dimless_Na_i</ci>

    <apply>
      <divide />
      <ci>cNa_i</ci>
      <apply><times />
      <ci>eq_Na_base_i</ci>
      <apply><exp />
      <apply><divide />
      <apply><times />
      <ci>partition_factor</ci>
      <ci>faraday_const</ci>
      <cn cellml:units="dimensionless">0.001</cn>
      <ci>Vm</ci>
    </apply>
    <apply><times />
    <cn cellml:units="dimensionless">3.0</cn>
    <ci>gas_const</ci>
    <ci>body_temp</ci>
  </apply>
</math>

```

```

    </apply>
  </apply>
</math>

```

```

<!-- calculate dimless_Na_e -->

```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#dimless_Na_e">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the dimless_Na_e parameter which is a
        function of Vm because the equilibrium constant is
        dependent on Vm (which occurs in the denominator's exponential). Note that the pa
        voltage dependency in the exponential corresponds to the previous calculation of
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dimless_Na_e_calc"><eq />
    <ci>dimless_Na_e</ci>

    <apply>
      <divide />
      <ci>cNa_e</ci>
      <apply><times />
      <ci>eq_Na_base_e</ci>
      <apply><exp />
      <apply><divide />
      <apply><times />
      <apply><plus />
      <cn cellml:units="dimensionless">1.</cn>
      <ci>partition_factor</ci>
      </apply>
      <ci>faraday_const</ci>
      <cn cellml:units="dimensionless">0.001</cn>
      <ci>Vm</ci>
      </apply>
      <apply><times />
      <cn cellml:units="dimensionless">3.0</cn>
      <ci>gas_const</ci>
      <ci>body_temp</ci>
      </apply>
    </apply>
  </apply>
</math>

```

```

<!-- calculate dimless_K_i -->

```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#dimless_K_i">

```

```

    <meta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the dimless_K_i parameter.
      </rdf:value>
    </meta:comment>
  </rdf:Description>
</rdf:RDF>

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dimless_K_i_calc"><eq />
    <ci>dimless_K_i</ci>
    <apply>
      <divide />
      <ci>cK_i</ci>
      <ci>eq_K_i</ci>
    </apply>
  </apply>
</math>

<!-- calculate dimless_K_e -->

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#dimless_K_e">
    <meta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the dimless_K_e parameter.
      </rdf:value>
    </meta:comment>
  </rdf:Description>
</rdf:RDF>

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dimless_K_e_calc"><eq />
    <ci>dimless_K_e</ci>
    <apply>
      <divide />
      <ci>cK_e</ci>
      <ci>eq_K_e</ci>
    </apply>
  </apply>
</math>

<!-- calculate dimless_MgATP -->

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#dimless_MgATP">
    <meta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the dimless_MgATP parameter.
      </rdf:value>
    </meta:comment>
  </rdf:Description>
</rdf:RDF>

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="dimless_MgATP_calc"><eq />
    <ci>dimless_MgATP</ci>

```

```

    <apply>
      <divide />
      <ci>cMgATP</ci>
      <ci>eq_MgATP</ci>
    </apply>
  </apply>
</math>

```

```

<!-- now the transition rates: calculate alpha -->

```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
  <rdf:Description rdf:about="#alpha">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the forward transition rate called alpha from the first to the second
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="alpha_calc"><eq />
    <ci>alpha</ci>

    <apply><divide />
      <apply><times />
        <ci>k1</ci>
      <apply><power />
        <ci>dimless_Na_i</ci>
        <cn cellml:units="dimensionless">3</cn>
      </apply>
    </apply>

    <apply><minus />
      <apply><plus />
        <apply><power />
          <apply><plus />
            <cn cellml:units="dimensionless">1.0</cn>
            <ci>dimless_Na_i</ci>
          </apply>
          <cn cellml:units="dimensionless">3</cn>
        </apply>
        <apply><power />
          <apply><plus />
            <cn cellml:units="dimensionless">1.0</cn>
            <ci>dimless_K_i</ci>
          </apply>
          <cn cellml:units="dimensionless">2</cn>
        </apply>
      </apply>
    <cn cellml:units="dimensionless">1.0</cn>
  </apply>
</math>

```

```
<!-- calculate alpha2 -->
```

```
<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#alpha2">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the forward transition rate called alpha2 from the second to the third state.
        Note that this transition rate is identical to k2 because state P7 (see paper) is not a lumped state.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>
```

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="alpha2_calc"><eq />
    <ci>alpha2</ci>
    <ci>k2</ci>
  </apply>
</math>
```

```
<!-- calculate alpha3 -->
```

```
<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#alpha3">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the forward transition rate called alpha3 from the third to the fourth state.
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>
```

```
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="alpha3_calc"><eq />
    <ci>alpha3</ci>
    <apply><divide />
      <apply><times />
        <ci>k3</ci>
      <apply><power />
        <ci>dimless_K_e</ci>
        <cn cellml:units="dimensionless">2</cn>
      </apply>
    </apply>
    <apply><minus />
      <apply><plus />
        <apply><power />
          <apply><plus />
            <cn cellml:units="dimensionless">1.0</cn>
            <ci>dimless_Na_e</ci>
          </apply>
          <cn cellml:units="dimensionless">3</cn>
        </apply>
        <apply><power />
          <apply><plus />
            <cn cellml:units="dimensionless">1.0</cn>
          </apply>
        </apply>
      </apply>
    </apply>
  </math>
```

```

        <ci>dimless_K_e</ci>
      </apply>
      <cn cellml:units="dimensionless">2</cn>
    </apply>
  </apply>
  <cn cellml:units="dimensionless">1.0</cn>
</apply>
</math>

<!-- calculate alpha4 -->

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#alpha4">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the foward transition rate called alpha4 from the fourth to the fi
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="alpha4_calc"><eq />
    <ci>alpha4</ci>
    <apply><divide />
      <apply><times />
        <ci>k4</ci>
        <ci>dimless_MgATP</ci>
      </apply>
    <apply><plus />
      <cn cellml:units="dimensionless">1.0</cn>
      <ci>dimless_MgATP</ci>
    </apply>
  </apply>
</math>

<!-- now the reverse recation rates: calculate minus_alpha1 -->

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
  <rdf:Description rdf:about="#minus_alpha1">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the reverse transition rate called minus_alpha1 from the second to
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="minus_alpha1_calc"><eq />
    <ci>minus_alpha1</ci>
    <apply><times />

```

```

        <ci>minus_k1</ci>
        <ci>cMgADP</ci>
    </apply>
</apply>
</math>

```

```

<!-- calculate minus_alpha2 -->

```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
<rdf:Description rdf:about="#minus_alpha2">
    <cmeta:comment rdf:parseType="Resource">
        <rdf:value>
            Calculation of the reverse transition rate called minus_alpha2 from the 3rd to th
        </rdf:value>
    </cmeta:comment>
</rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply id="minus_alpha2_calc"><eq />
        <ci>minus_alpha2</ci>

        <apply><divide />
            <apply><times />
                <ci>minus_k2</ci>
            <apply><power />
                <ci>dimless_Na_e</ci>
                <cn cellml:units="dimensionless">3</cn>
            </apply>
        </apply>

        <apply><minus />
            <apply><plus />
                <apply><power />
                    <apply><plus />
                        <cn cellml:units="dimensionless">1.0</cn>
                        <ci>dimless_Na_e</ci>
                    </apply>
                    <cn cellml:units="dimensionless">3</cn>
                </apply>
                <apply><power />
                    <apply><plus />
                        <cn cellml:units="dimensionless">1.0</cn>
                        <ci>dimless_K_e</ci>
                    </apply>
                    <cn cellml:units="dimensionless">2</cn>
                </apply>
            </apply>
            <cn cellml:units="dimensionless">1.0</cn>
        </apply>
    </apply>
</math>

```

```

<!-- calculate minus_alpha3 -->

```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
<rdf:Description rdf:about="#minus_alpha3">
  <cmeta:comment rdf:parseType="Resource">
    <rdf:value>
      Calculation of the reverse transition rate called minus_alpha3 from the fourth to
    </rdf:value>
  </cmeta:comment>
</rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
<apply id="minus_alpha3_calc"><eq />
  <ci>minus_alpha3</ci>
  <apply><divide />
    <apply><times />
      <ci>minus_k3</ci>
      <ci>cPi</ci>
      <ci>cH</ci>
    </apply>
  </apply><plus />
  <cn cellml:units="dimensionless">1.0</cn>
  <ci>dimless_MgATP</ci>
</apply>
</math>

```

```

<!-- calculate minus_alpha4 -->

```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
<rdf:Description rdf:about="#minus_alpha4">
  <cmeta:comment rdf:parseType="Resource">
    <rdf:value>
      Calculation of the reverse transition rate called minus_alpha4 from the first to
    </rdf:value>
  </cmeta:comment>
</rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
<apply id="minus_alpha4_calc"><eq />
  <ci>minus_alpha4</ci>
  <apply><divide />
    <apply><times />
      <ci>minus_k4</ci>
    </apply><power />
    <ci>dimless_K_i</ci>
    <cn cellml:units="dimensionless">2</cn>
  </apply>
  <apply><minus />
    <apply><plus />
      <apply><power />
        <apply><plus />

```

```

        <cn cellml:units="dimensionless">1.0</cn>
        <ci>dimless_Na_i</ci>
    </apply>
    <cn cellml:units="dimensionless">3</cn>
</apply>
<apply><power />
  <apply><plus />
    <cn cellml:units="dimensionless">1.0</cn>
    <ci>dimless_K_i</ci>
  </apply>
  <cn cellml:units="dimensionless">2</cn>
</apply>
</apply>
  <cn cellml:units="dimensionless">1.0</cn>
</apply>
</math>

```

*<!-- now we can calculate the denominator of the clockwise cycle rate v\_cyc which is the sum of the cycle rates v\_cyc1, v\_cyc2, and v\_cyc3 -->*

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
  <rdf:Description rdf:about="#diagram_sum">
    <cmeta:comment rdf:parseType="Resource">
      <rdf:value>
        Calculation of the diagram sum used in the denominator of the equation of cycle rate v_cyc
      </rdf:value>
    </cmeta:comment>
  </rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="diagram_sum"><eq />
    <ci>diagram_sum</ci>

    <apply><plus />
      <apply><times />
        <ci>minus_alpha3</ci>
        <ci>minus_alpha2</ci>
        <ci>minus_alpha1</ci>
      </apply>
      <apply><times />
        <ci>alpha4</ci>
        <ci>minus_alpha2</ci>
        <ci>minus_alpha1</ci>
      </apply>
      <apply><times />
        <ci>alpha4</ci>
        <ci>alpha2</ci>
        <ci>alpha3</ci>
      </apply>
      <apply><times />
        <ci>alpha4</ci>
        <ci>minus_alpha1</ci>
        <ci>alpha3</ci>
      </apply>
  </math>

```

```

<apply><times />
  <ci>minus_alpha3</ci>
  <ci>minus_alpha2</ci>
  <ci>alpha1</ci>
</apply>
<apply><times />
  <ci>alpha4</ci>
  <ci>minus_alpha2</ci>
  <ci>alpha1</ci>
</apply>
<apply><times />
  <ci>alpha4</ci>
  <ci>alpha1</ci>
  <ci>alpha3</ci>
</apply>
<apply><times />
  <ci>minus_alpha3</ci>
  <ci>alpha1</ci>
  <ci>alpha2</ci>
</apply>

<apply><times />
  <ci>alpha4</ci>
  <ci>alpha1</ci>
  <ci>alpha2</ci>
</apply>
<apply><times />
  <ci>alpha1</ci>
  <ci>alpha2</ci>
  <ci>alpha3</ci>
</apply>
<apply><times />
  <ci>minus_alpha4</ci>
  <ci>minus_alpha3</ci>
  <ci>minus_alpha1</ci>
</apply>
<apply><times />
  <ci>minus_alpha4</ci>
  <ci>minus_alpha3</ci>
  <ci>alpha2</ci>
</apply>

<apply><times />
  <ci>minus_alpha4</ci>
  <ci>minus_alpha3</ci>
  <ci>minus_alpha2</ci>
</apply>
<apply><times />
  <ci>minus_alpha4</ci>
  <ci>minus_alpha1</ci>
  <ci>minus_alpha2</ci>
</apply>
<apply><times />
  <ci>minus_alpha4</ci>
  <ci>alpha2</ci>
  <ci>alpha3</ci>
</apply>
<apply><times />
  <ci>minus_alpha4</ci>

```

```

        <ci>minus_alpha1</ci>
        <ci>alpha3</ci>
    </apply>

</apply>
</apply>
</math>

```

```

<!-- calculate clockwise cycle rate v_cyc-->

```

```

<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
<rdf:Description rdf:about="#v_cyc">
  <cmeta:comment rdf:parseType="Resource">
    <rdf:value>
      Calculation of the clockwise cycle rate v_cyc.
    </rdf:value>
  </cmeta:comment>
</rdf:Description>
</rdf:RDF>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply id="v_cyc_calc"><eq />
    <ci>v_cyc</ci>

    <apply><divide />
      <apply><minus />
        <apply><times />
          <ci>alpha1</ci>
        <ci>alpha2</ci>
        <ci>alpha3</ci>
      <ci>alpha4</ci>
    </apply>
    <apply><times />
      <ci>minus_alpha1</ci>
      <ci>minus_alpha2</ci>
      <ci>minus_alpha3</ci>
      <ci>minus_alpha4</ci>
    </apply>
    <ci>diagram_sum</ci>
  </apply>
</math>

```

```

</component><!--EO NaK_pump-->

```

```

<!--Connections and relationships between components-->

```

```

<connection>
  <map_components component_1="interface" component_2="NaK_pump" />
  <map_variables variable_1="Vm" variable_2="Vm" />
  <map_variables variable_1="cNa_i" variable_2="cNa_i" />
  <map_variables variable_1="v_cyc" variable_2="v_cyc" />
  <map_variables variable_1="net_free_energy" variable_2="net_free_energy" />
  <map_variables variable_1="cMgADP" variable_2="cMgADP" />
</connection>

```

```
<group>
  <relationship_ref relationship="encapsulation" />
  <component_ref component="interface">
    <component_ref component="NaK_pump" />
  </component_ref>
</group>

</model>
```