SBML Model Report

Model name: “Kongas2007 - Creatine Kinase in energy metabolic signaling in muscle”

May 5, 2016

1 General Overview

This is a document in SBML Level 2 Version 1 format. This model was created by the following three authors: Nicolas Le Novre[1], Maria Schilstra[2] and Rainer Machne[3] at June 29th 2005 at 12:27 a. m. and last time modified at October tenth 2014 at 10:18 a. m. Table 1 gives an overview of the quantities of all components of this model.

Table 1: Number of components in this model, which are described in the following sections.

Element	Quantity	Element	Quantity
compartment types	0	compartments	2
species types	0	species	10
events	0	constraints	0
reactions	9	function definitions	0
global parameters	0	unit definitions	1
rules	0	initial assignments	0

Model Notes

Kongas2007 - Creatine Kinase in energy metabolic signaling in muscle

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This model is described in the article:Creatine kinase in energy metabolic signaling in muscleOlav Kongas and Johannes H. G. M. van BeekAvailable from Nature Precedings

Abstract:

There has been much debate on the mechanism of regulation of mitochondrial ATP synthesis to balance ATP consumption during changing cardiac workloads. A key role of creatine kinase (CK) isoenzymes in this regulation of oxidative phosphorylation and in intracellular energy transport had been proposed, but has in the mean time been disputed for many years. It was hypothesized that high-energy phosphorylgroups are obligatorily transferred via CK; this is termed the phosphocreatine shuttle. The other important role ascribed to the CK system is its ability to buffer ADP concentration in cytosol near sites of ATP hydrolysis.

Almost all of the experiments to determine the role of CK had been done in the steady state, but recently the dynamic response of oxidative phosphorylation to quick changes in cytosolic ATP hydrolysis has been assessed at various levels of inhibition of CK. Steady state models of CK function in energy transfer existed but were unable to explain the dynamic response with CK inhibited.

The aim of this study was to explain the mode of functioning of the CK system in heart, and in particular the role of different CK isoenzymes in the dynamic response to workload steps. For this purpose we used a mathematical model of cardiac muscle cell energy metabolism containing the kinetics of the key processes of energy production, consumption and transfer pathways. The model underscores that CK plays indeed a dual role in the cardiac cells. The buffering role of CK system is due to the activity of myofibrillar CK (MMCK) while the energy transfer role depends on the activity of mitochondrial CK (MiCK). We propose that this may lead to the differences in regulation mechanisms and energy transfer modes in species with relatively low MiCK activity such as rabbit in comparison with species with high MiCK activity such as rat.

The model needed modification to explain the new type of experimental data on the dynamic response of the mitochondria. We submit that building a Virtual Muscle Cell is not possible without continuous experimental tests to improve the model. In close interaction with experiments we are developing a model for muscle energy metabolism and transport mediated by the creatine kinase isoforms which now already can explain many different types of experiments.

The model has been designed according to the spirit of the paper. The list of rate in the appendix has been corrected as follow:

1. d[ATP]/dt = (-Vhyd -Vmmck +Jatp) / Vcyt
2. d[ADP]/dt = (Vhyd +Vmmck +Jadp) / Vcyt
3. d[PCr]/dt = (Vmmck +Jpcr) / Vcyt
4. d[Cr]/dt = (-Vmmck +Jpcr) / Vcyt
5. d[Pi]/dt = (Vhyd + Jpi) / Vcyt
6. d[ATPi]/dt = (+Vsyn -Vmick -Jatp) / Vims
7. d[ADPi]/dt = (-Vsyn +Vmick -Jadp) / Vims

8. d[PCri]/dt = (Vmick -Jpcr) / Vims
9. d[Cri]/dt = (-Vmick -Jpcr) / Vims
10. d[Pii]/dt = (-Vsyn -Jpi) / Vims

This model is hosted on BioModels Database and identified by: BIOMD0000000041 .

To cite BioModels Database, please use: BioModels Database: An enhanced, curated and annotated resource for published quantitative kinetic models .

2 Unit Definitions

This is an overview of five unit definitions of which four are predefined by SBML and not mentioned in the model.

2.1 Unit `substance`

Name micromole

Definition µmol

2.2 Unit `volume`

Notes Litre is the predefined SBML unit for `volume`.

Definition l

2.3 Unit `area`

Notes Square metre is the predefined SBML unit for `area` since SBML Level 2 Version 1.

Definition m^2

2.4 Unit `length`

Notes Metre is the predefined SBML unit for `length` since SBML Level 2 Version 1.

Definition m

2.5 Unit `time`

Notes Second is the predefined SBML unit for `time`.

Definition s

3 Compartments

This model contains two compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
IMS			3	0.0625	l	☑	
CYT			3	0.75	l	☑	

3.1 Compartment IMS

This is a three dimensional compartment with a constant size of 0.0625 litre.

3.2 Compartment CYT

This is a three dimensional compartment with a constant size of 0.75 litre.

4 Species

This model contains ten species. Section 6 provides further details and the derived rates of change of each species.

Table 3: Properties of each species.

Id	Name	Compartment	Derived Unit	Constant	Boundary Condition
ADPi		IMS	$\mu mol \cdot l^{-1}$	⊟	⊟
ATPi		IMS	$\mu mol \cdot l^{-1}$	⊟	⊟
Cri		IMS	$\mu mol \cdot l^{-1}$	⊟	⊟
PCri		IMS	$\mu mol \cdot l^{-1}$	⊟	⊟
PCr		CYT	$\mu mol \cdot l^{-1}$	⊟	⊟
ADP		CYT	$\mu mol \cdot l^{-1}$	⊟	⊟
ATP		CYT	$\mu mol \cdot l^{-1}$	⊟	⊟
Cr		CYT	$\mu mol \cdot l^{-1}$	⊟	⊟
Pi	Pii	IMS	$\mu mol \cdot l^{-1}$	⊟	⊟
P	Pi	CYT	$\mu mol \cdot l^{-1}$	⊟	⊟

5 Reactions

This model contains nine reactions. All reactions are listed in the following table and are subsequently described in detail. If a reaction is affected by a modifier, the identifier of this species is written above the reaction arrow.

Table 4: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	`OxPhos`	Vsyn	$\mathrm{ADPi} + \mathrm{Pi} \rightleftharpoons \mathrm{ATPi}$	
2	`MiCK`	Vmick	$\mathrm{ATPi} + \mathrm{Cri} \rightleftharpoons \mathrm{ADPi} + \mathrm{PCri}$	
3	`MMCK`	Vmmck	$\mathrm{ATP} + \mathrm{Cr} \rightleftharpoons \mathrm{PCr} + \mathrm{ADP}$	
4	`ATPase`	Vhyd	$\mathrm{ATP} \longrightarrow \mathrm{ADP} + \mathrm{P}$	
5	`Pi_diffusion`	Jpi	$\mathrm{Pi} \rightleftharpoons \mathrm{P}$	
6	`Cr_diffusion`	Jcr	$\mathrm{Cri} \rightleftharpoons \mathrm{Cr}$	
7	`ADP_diffusion`	Jadp	$\mathrm{ADPi} \rightleftharpoons \mathrm{ADP}$	
8	`PCr_diffusion`	Jpcr	$\mathrm{PCri} \rightleftharpoons \mathrm{PCr}$	
9	`ATP_diffusion`	Jatp	$\mathrm{ATPi} \rightleftharpoons \mathrm{ATP}$	

5.1 Reaction OxPhos

This is a reversible reaction of two reactants forming one product.

Name Vsyn

Reaction equation

$$\mathrm{ADPi} + \mathrm{Pi} \rightleftharpoons \mathrm{ATPi} \tag{1}$$

Reactants

Table 5: Properties of each reactant.

Id	Name	SBO
ADPi		
Pi	Pii	

Product

Table 6: Properties of each product.

Id	Name	SBO
ATPi		

Kinetic Law

Derived unit contains undeclared units

$$v_1 = \mathrm{vol}\,(\mathrm{IMS}) \cdot \frac{\mathrm{V\_1} \cdot [\mathrm{ADPi}] \cdot [\mathrm{Pi}]}{\mathrm{Ka\_1} \cdot \mathrm{Kb\_1} \cdot \left(1 + \frac{[\mathrm{ADPi}]}{\mathrm{Ka\_1}} + \frac{[\mathrm{Pi}]}{\mathrm{Kb\_1}} + \frac{[\mathrm{ADPi}] \cdot [\mathrm{Pi}]}{\mathrm{Ka\_1} \cdot \mathrm{Kb\_1}}\right)} \tag{2}$$

Table 7: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
V_1	Vsynmax		4600.0		☑
Ka_1	Kadp		800.0		☑
Kb_1	Kpi		20.0		☑

5.2 Reaction MiCK

This is a reversible reaction of two reactants forming two products.

Name Vmick

Reaction equation

$$\mathrm{ATPi} + \mathrm{Cri} \rightleftharpoons \mathrm{ADPi} + \mathrm{PCri} \tag{3}$$

Reactants

Table 8: Properties of each reactant.

Id	Name	SBO
ATPi		
Cri		

Products

Table 9: Properties of each product.

Id	Name	SBO
ADPi		
PCri		

Kinetic Law

Derived unit contains undeclared units

$$v_2 = \mathrm{vol}\,(\mathrm{IMS}) \cdot \frac{\frac{\mathrm{Vf\_2}\cdot[\mathrm{ATPi}]\cdot[\mathrm{Cri}]}{\mathrm{Kia\_2}\cdot\mathrm{Kb\_2}} - \frac{\mathrm{Vb\_2}\cdot[\mathrm{ADPi}]\cdot[\mathrm{PCri}]}{\mathrm{Kic\_2}\cdot\mathrm{Kd\_2}}}{1 + \frac{[\mathrm{Cri}]}{\mathrm{Kib\_2}} + \frac{[\mathrm{PCri}]}{\mathrm{Kid\_2}} + [\mathrm{ATPi}]\cdot\left(\frac{1}{\mathrm{Kia\_2}} + \frac{[\mathrm{Cri}]}{\mathrm{Kia\_2}\cdot\mathrm{Kb\_2}}\right) + [\mathrm{ADPi}]\cdot\left(\frac{1}{\mathrm{Kic\_2}} + \frac{[\mathrm{Cri}]}{\mathrm{Kic\_2}\cdot\mathrm{Kib\_2}} + \frac{[\mathrm{PCri}]}{\mathrm{Kid\_2}\cdot\frac{\mathrm{Kic\_2}\cdot\mathrm{Kd\_2}}{\mathrm{Kid\_2}}}\right)} \tag{4}$$

Table 10: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
Vf_2			2658.0		☑
Kia_2			750.0		☑
Kb_2			5200.0		☑
Vb_2			11160.0		☑

Id	Name	SBO	Value	Unit	Constant
Kic_2			204.8		☑
Kd_2			500.0		☑
Kib_2			28800.0		☑
Kid_2			1600.0		☑

5.3 Reaction MMCK

This is a reversible reaction of two reactants forming two products.

Name Vmmck

Reaction equation

$$\mathrm{ATP} + \mathrm{Cr} \rightleftharpoons \mathrm{PCr} + \mathrm{ADP} \tag{5}$$

Reactants

Table 11: Properties of each reactant.

Id	Name	SBO
ATP		
Cr		

Products

Table 12: Properties of each product.

Id	Name	SBO
PCr		
ADP		

Kinetic Law

Derived unit contains undeclared units

$$v_3 = \mathrm{vol}\,(\mathrm{CYT}) \cdot \frac{\frac{\mathrm{Vf\_3}\cdot[\mathrm{ATP}]\cdot[\mathrm{Cr}]}{\mathrm{Kia\_3}\cdot\mathrm{Kb\_3}} - \frac{\mathrm{Vb\_3}\cdot[\mathrm{ADP}]\cdot[\mathrm{PCr}]}{\mathrm{Kic\_3}\cdot\mathrm{Kd\_3}}}{1 + \frac{[\mathrm{Cr}]}{\mathrm{Kib\_3}} + \frac{[\mathrm{PCr}]}{\mathrm{Kid\_3}} + [\mathrm{ATP}]\cdot\left(\frac{1}{\mathrm{Kia\_3}} + \frac{[\mathrm{Cr}]}{\mathrm{Kia\_3}\cdot\mathrm{Kb\_3}}\right) + [\mathrm{ADP}]\cdot\left(\frac{1}{\mathrm{Kic\_3}} + \frac{[\mathrm{Cr}]}{\mathrm{Kic\_3}\cdot\mathrm{Kib\_3}} + \frac{[\mathrm{PCr}]}{\mathrm{Kid\_3}\cdot\frac{\mathrm{Kic\_3}\cdot\mathrm{Kd\_3}}{\mathrm{Kid\_3}}}\right)} \tag{6}$$

Table 13: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
Vf_3			6966.0		☑
Kia_3			900.0		☑
Kb_3			15500.0		☑
Vb_3			29250.0		☑
Kic_3			222.4		☑
Kd_3			1670.0		☑
Kib_3			34900.0		☑
Kid_3			4730.0		☑

5.4 Reaction ATPase

This is an irreversible reaction of one reactant forming two products.

Name Vhyd

Reaction equation

$$\mathrm{ATP} \longrightarrow \mathrm{ADP} + \mathrm{P} \tag{7}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
ATP		

Products

Table 15: Properties of each product.

Id	Name	SBO
ADP		
P	Pi	

Kinetic Law

Derived unit contains undeclared units

$$v_4 = \mathrm{vol}\,(\mathrm{CYT}) \cdot \mathrm{v\_4} \cdot [\mathrm{ATP}] \tag{8}$$

Table 16: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
v_4	Vhyd		4600.0		☑

5.5 Reaction Pi_diffusion

This is a reversible reaction of one reactant forming one product.

Name Jpi

Reaction equation

$$\mathrm{Pi} \rightleftharpoons \mathrm{P} \tag{9}$$

Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
Pi	Pii	

Product

Table 18: Properties of each product.

Id	Name	SBO
P	Pi	

Kinetic Law

Derived unit contains undeclared units

$$v_5 = \mathrm{vol}\,(\mathrm{IMS}) \cdot \mathrm{k2\_5} \cdot [\mathrm{Pi}] - \mathrm{vol}\,(\mathrm{CYT}) \cdot \mathrm{k2\_5} \cdot [\mathrm{P}] \tag{10}$$

Table 19: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k2_5	Rpi		18.4		☑

5.6 Reaction Cr_diffusion

This is a reversible reaction of one reactant forming one product.

Name Jcr

Reaction equation

$$\mathrm{Cri} \rightleftharpoons \mathrm{Cr} \tag{11}$$

Reactant

Table 20: Properties of each reactant.

Id	Name	SBO
Cri		

Product

Table 21: Properties of each product.

Id	Name	SBO
Cr		

Kinetic Law

Derived unit contains undeclared units

$$v_6 = \mathrm{vol}\left(\mathrm{IMS}\right) \cdot \mathrm{k1\_6} \cdot [\mathrm{Cri}] - \mathrm{vol}\left(\mathrm{CYT}\right) \cdot \mathrm{k1\_6} \cdot [\mathrm{Cr}] \tag{12}$$

Table 22: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1_6	Rcr		14.6		☑

5.7 Reaction ADP_diffusion

This is a reversible reaction of one reactant forming one product.

Name Jadp

Reaction equation

$$\mathrm{ADPi} \rightleftharpoons \mathrm{ADP} \tag{13}$$

Reactant

Table 23: Properties of each reactant.

Id	Name	SBO
ADPi		

Product

Table 24: Properties of each product.

Id	Name	SBO
ADP		

Kinetic Law

Derived unit contains undeclared units

$$v_7 = \mathrm{vol}\,(\mathrm{IMS}) \cdot \mathrm{k1\_7} \cdot [\mathrm{ADPi}] - \mathrm{vol}\,(\mathrm{CYT}) \cdot \mathrm{k1\_7} \cdot [\mathrm{ADP}] \tag{14}$$

Table 25: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1_7	Radp		8.16		☑

5.8 Reaction PCr_diffusion

This is a reversible reaction of one reactant forming one product.

Name Jpcr

Reaction equation

$$\mathrm{PCri} \rightleftharpoons \mathrm{PCr} \tag{15}$$

Reactant

Table 26: Properties of each reactant.

Id	Name	SBO
PCri		

Product

Table 27: Properties of each product.

Id	Name	SBO
PCr		

Kinetic Law

Derived unit contains undeclared units

$$v_8 = \mathrm{vol}\,(\mathrm{IMS}) \cdot \mathrm{k1\_8} \cdot [\mathrm{PCri}] - \mathrm{vol}\,(\mathrm{CYT}) \cdot \mathrm{k1\_8} \cdot [\mathrm{PCr}] \tag{16}$$

Table 28: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1_8	Jpcr		14.6		☑

5.9 Reaction ATP_diffusion

This is a reversible reaction of one reactant forming one product.

Name Jatp

Reaction equation

$$\mathrm{ATPi} \rightleftharpoons \mathrm{ATP} \tag{17}$$

Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
ATPi		

Product

Table 30: Properties of each product.

Id	Name	SBO
ATP		

Kinetic Law

Derived unit contains undeclared units

$$v_9 = \mathrm{vol}\,(\mathrm{IMS}) \cdot \mathrm{k1\_9} \cdot [\mathrm{ATPi}] - \mathrm{vol}\,(\mathrm{CYT}) \cdot \mathrm{k1\_9} \cdot [\mathrm{ATP}] \tag{18}$$

Table 31: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
k1_9	Jatp		8.16		☑

6 Derived Rate Equations

When interpreted as an ordinary differential equation framework, this model implies the following set of equations for the rates of change of each species.

Identifiers for kinetic laws highlighted in gray cannot be verified to evaluate to units of SBML `substance` per `time`. As a result, some SBML interpreters may not be able to verify the consistency of the units on quantities in the model. Please check if

- parameters without an unit definition are involved or
- volume correction is necessary because the `hasOnlySubstanceUnits` flag may be set to `false` and `spacialDimensions`> 0 for certain species.

6.1 Species ADPi

Initial concentration $0\ \mu\mathrm{mol} \cdot \mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in OxPhos, ADP_diffusion and as a product in MiCK).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ADPi} = v_2 - v_1 - v_7 \tag{19}$$

6.2 Species ATPi

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in three reactions (as a reactant in MiCK, ATP_diffusion and as a product in OxPhos).

$$\frac{\text{d}}{\text{d}t}\text{ATPi} = v_1 - v_2 - v_9 \tag{20}$$

6.3 Species Cri

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in MiCK, Cr_diffusion).

$$\frac{\text{d}}{\text{d}t}\text{Cri} = -v_2 - v_6 \tag{21}$$

6.4 Species PCri

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in PCr_diffusion and as a product in MiCK).

$$\frac{\text{d}}{\text{d}t}\text{PCri} = v_2 - v_8 \tag{22}$$

6.5 Species PCr

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a product in MMCK, PCr_diffusion).

$$\frac{\text{d}}{\text{d}t}\text{PCr} = v_3 + v_8 \tag{23}$$

6.6 Species ADP

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in three reactions (as a product in MMCK, ATPase, ADP_diffusion).

$$\frac{\text{d}}{\text{d}t}\text{ADP} = v_3 + v_4 + v_7 \tag{24}$$

6.7 Species ATP

Initial concentration $9700\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in three reactions (as a reactant in MMCK, ATPase and as a product in ATP_diffusion).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{ATP} = v_9 - v_3 - v_4 \tag{25}$$

6.8 Species Cr

Initial concentration $26000\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in MMCK and as a product in Cr_diffusion).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Cr} = v_6 - v_3 \tag{26}$$

6.9 Species Pi

Name Pii

Initial concentration $32000\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a reactant in OxPhos, Pi_diffusion).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Pi} = -v_1 - v_5 \tag{27}$$

6.10 Species P

Name Pi

Initial concentration $0\ \mu\text{mol}\cdot\text{l}^{-1}$

This species takes part in two reactions (as a product in ATPase, Pi_diffusion).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{P} = v_4 + v_5 \tag{28}$$

SBML2LaTeX was developed by Andreas Dräger[a], Hannes Planatscher[a], Dieudonné M Wouamba[a], Adrian Schröder[a], Michael Hucka[b], Lukas Endler[c], Martin Golebiewski[d] and Andreas Zell[a]. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

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