SBML Model Report

Model name: “Cursons2015 - Regulation of ERK-MAPK signaling in human epidermis”

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1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Kun Yang[1], Rahuman Sheriff[2] and Emma Louise Fairbanks[3] at June 22nd 2017 at 9:52 a. m. and last time modified at November second 2017 at 11:35 a. m. Table 1 shows 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	7
events	5	constraints	0
reactions	0	function definitions	0
global parameters	25	unit definitions	2
rules	13	initial assignments	0

Model Notes

Cursons2015 - Regulation of ERK-MAPKsignaling in human epidermisModel comparing the abundance ofphosphorylated MAPK signalling proteins and calcium signalling inthe epidermis.

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This model is described in the article:Regulation of ERK-MAPK signaling in human epidermis.Cursons J, Gao J, Hurley DG, Print CG, Dunbar PR, Jacobs MD, Crampin EJ.BMC Syst Biol 2015; 9: 41

Abstract:

The skin is largely comprised of keratinocytes within the interfollicular epidermis. Over approximately two weeks these cells differentiate and traverse the thickness of the skin. The stage of differentiation is therefore reflected in the positions of cells within the tissue, providing a convenient axis along which to study the signaling events that occur in situ during keratinocyte terminal differentiation, over this extended two-week timescale. The canonical ERK-MAPK signaling cascade (Raf-1, MEK-1/2 and ERK-1/2) has been implicated in controlling diverse cellular behaviors, including proliferation and differentiation. While the molecular interactions involved in signal transduction through this cascade have been well characterized in cell culture experiments, our understanding of how this sequence of events unfolds to determine cell fate within a homeostatic tissue environment has not been fully characterized.We measured the abundance of total and phosphorylated ERK-MAPK signaling proteins within interfollicular keratinocytes in transverse cross-sections of human epidermis using immunofluorescence microscopy. To investigate these data we developed a mathematical model of the signaling cascade using a normalized-Hill differential equation formalism.These data show coordinated variation in the abundance of phosphorylated ERK-MAPK components across the epidermis. Statistical analysis of these data shows that associations between phosphorylated ERK-MAPK components which correspond to canonical molecular interactions are dependent upon spatial position within the epidermis. The model demonstrates that the spatial profile of activation for ERK-MAPK signaling components across the epidermis may be maintained in a cell-autonomous fashion by an underlying spatial gradient in calcium signaling.Our data demonstrate an extended phosphoprotein profile of ERK-MAPK signaling cascade components across the epidermis in situ, and statistical associations in these data indicate canonical ERK-MAPK interactions underlie this spatial profile of ERK-MAPK activation. Using mathematical modelling we have demonstrated that spatially varying calcium signaling components across the epidermis may be sufficient to maintain the spatial profile of ERK-MAPK signaling cascade components in a cell-autonomous manner. These findings may have significant implications for the wide range of cancer drugs which therapeutically target ERK-MAPK signaling components.

This model is hosted on BioModels Database and identified by: BIOMD0000000659.

To cite BioModels Database, please use: Chelliah V et al. BioModels: ten-year anniversary. Nucl. Acids Res. 2015, 43(Database issue):D542-8.

2 Unit Definitions

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

2.1 Unit substance

Name substance

Definition mmol

2.2 Unit unit_0

Name 1

Definition dimensionless^{0}

2.3 Unit volume

Notes Litre is the predefined SBML unit for volume.

Definition l

2.4 Unit area

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

Definition m^{2}

2.5 Unit length

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

Definition m

2.6 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
c	cytoplasm		3	1	litre	☑	
n	nucleus		3	0.5	l	☑	

3.1 Compartment c

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

Name cytoplasm

3.2 Compartment n

This is a three dimensional compartment with a constant size of 0.5 litre.

Name nucleus

4 Species

This model contains seven species. The boundary condition of seven of these species is set to `true` so that these species' amount cannot be changed by any reaction. Section 8 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
`pRaf_cyto`	Rafc	`c`	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑
`pMEK_cyto`	MEKc	`c`	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑
`pERK_cyto`	ERKc	`c`	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑
`pMEK_nuc`	MEKn	`n`	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑
`pERK_nuc`	ERKn	`n`	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑
`Ca`	Ca	`c`	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑
`CaM_memb`	CaM	`c`	$\mathrm{mmol} \cdot \mathrm{l}^{-1}$	⊟	☑

5 Parameters

This model contains 25 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
numTissuePos	Tissue_Pos		0.500	dimensionless^0	☑
numCytoToNucVolRatio	Cyto_Nuc_VolRatio		2.357	dimensionless^0	☐
numCaInputBaseline	Ca_Baseline		0.754	dimensionless^0	☑
numCaInputAmp	Ca_Amp		0.092	dimensionless^0	☑
numCaMInputBaseline	CaM_Baseline		0.363	dimensionless^0	☑
numCaMInputAmp	CaM_Amp		0.485	dimensionless^0	☑
numHillCoeff	Hill_Coeff		1.400	dimensionless^0	☑
numHillWeight	Hill_Weight		1.000	dimensionless^0	☑
numHillMax	Hill_Max		1.000	dimensionless^0	☑
numHillTau	Hill_Tau		1.000	dimensionless^0	☑
numHillEC50	Hill_EC50		0.500	dimensionless^0	☑
numMEKCytoToNucRatio	MEK_CtoN		0.050	dimensionless^0	☑
numMEKNucToCytoRatio	MEK_NtoC		0.500	dimensionless^0	☑
numERKCytoToNucRatio	ERK_CtoN		0.010	dimensionless^0	☑
numERKNucToCytoRatio	ERK_NtoC		0.010	dimensionless^0	☑
numHillBeta	Hill_Beta		2.560	dimensionless^0	☑
numHillK	Hill_K		1.370	dimensionless^0	☑
funcHillCaToRaf	Hill_CaToRaf		0.783	dimensionless^0	☐
funcHillCaMToRaf	Hill_CaMToRaf		0.747	dimensionless^0	☐
funcHillERKToRaf	Hill_ERKToRaf		0.162	dimensionless^0	☐
funcHillRafToMEK	Hill_RafToMEK		0.502	dimensionless^0	☐
funcHillMEKToERKCyto	Hill_MEKToERKCyto		0.820	dimensionless^0	☐
funcHillMEKToERKNuc	Hill_MEKToERKNuc		0.388	dimensionless^0	☐
funcHillERKToERKn	Hill_ERKToERKn		0.162	dimensionless^0	☐
numTotalRafInputs	TotalRafInputs		0.000	dimensionless^0	☐

6 Rules

This is an overview of 13 rules.

6.1 Rule numCytoToNucVolRatio

Rule numCytoToNucVolRatio is an assignment rule for parameter numCytoToNucVolRatio:

$$\text{numCytoToNucVolRatio} = 2 + 5 \cdot \frac{\text{numTissuePos}}{7} \tag{1}$$

6.2 Rule funcHillCaToRaf

Rule funcHillCaToRaf is an assignment rule for parameter funcHillCaToRaf:

$$\text{funcHillCaToRaf} = \frac{\text{numHillWeight} \cdot \text{numHillBeta} \cdot [\text{Ca}]^{\text{numHillCoeff}}}{\text{numHillK}^{\text{numHillCoeff}} + [\text{Ca}]^{\text{numHillCoeff}}} \tag{2}$$

6.3 Rule funcHillCaMToRaf

Rule funcHillCaMToRaf is an assignment rule for parameter funcHillCaMToRaf:

$$\text{funcHillCaMToRaf} = \frac{\text{numHillWeight} \cdot \text{numHillBeta} \cdot [\text{CaM\_memb}]^{\text{numHillCoeff}}}{\text{numHillK}^{\text{numHillCoeff}} + [\text{CaM\_memb}]^{\text{numHillCoeff}}} \tag{3}$$

6.4 Rule funcHillERKToRaf

Rule funcHillERKToRaf is an assignment rule for parameter funcHillERKToRaf:

$$\text{funcHillERKToRaf} = \frac{\text{numHillWeight} \cdot \text{numHillBeta} \cdot [\text{pERK\_nuc}]^{\text{numHillCoeff}}}{\text{numHillK}^{\text{numHillCoeff}} + [\text{pERK\_nuc}]^{\text{numHillCoeff}}} \tag{4}$$

6.5 Rule funcHillRafToMEK

Rule funcHillRafToMEK is an assignment rule for parameter funcHillRafToMEK:

$$\text{funcHillRafToMEK} = \frac{\text{numHillWeight} \cdot \text{numHillBeta} \cdot [\text{pRaf\_cyto}]^{\text{numHillCoeff}}}{\text{numHillK}^{\text{numHillCoeff}} + [\text{pRaf\_cyto}]^{\text{numHillCoeff}}} \tag{5}$$

6.6 Rule funcHillMEKToERKCyto

Rule funcHillMEKToERKCyto is an assignment rule for parameter funcHillMEKToERKCyto:

$$\text{funcHillMEKToERKCyto} = \frac{\text{numHillWeight} \cdot \text{numHillBeta} \cdot [\text{pMEK\_cyto}]^{\text{numHillCoeff}}}{\text{numHillK}^{\text{numHillCoeff}} + [\text{pMEK\_cyto}]^{\text{numHillCoeff}}} \tag{6}$$

6.7 Rule funcHillMEKToERKNuc

Rule funcHillMEKToERKNuc is an assignment rule for parameter funcHillMEKToERKNuc:

$$\text{funcHillMEKToERKNuc} = \frac{\text{numHillWeight} \cdot \text{numHillBeta} \cdot [\text{pMEK\_nuc}]^{\text{numHillCoeff}}}{\text{numHillK}^{\text{numHillCoeff}} + [\text{pMEK\_nuc}]^{\text{numHillCoeff}}} \tag{7}$$

6.8 Rule `funcHillERKToERKNuc`

Rule `funcHillERKToERKNuc` is an assignment rule for parameter `funcHillERKToERKNuc`:

$$\text{funcHillERKToERKNuc} = \frac{\text{numHillWeight} \cdot \text{numHillBeta} \cdot [\text{pERK\_nuc}]^{\text{numHillCoeff}}}{\text{numHillK}^{\text{numHillCoeff}} + [\text{pERK\_nuc}]^{\text{numHillCoeff}}} \tag{8}$$

6.9 Rule `pRaf_cyto`

Rule `pRaf_cyto` is a rate rule for species `pRaf_cyto`:

$$\frac{\mathrm{d}}{\mathrm{d}t}\text{pRaf\_cyto} = \frac{1}{\text{numHillTau}} \cdot (\text{numTotalRafInputs} \cdot \text{numHillMax} - [\text{pRaf\_cyto}]) \tag{9}$$

6.10 Rule `pMEK_cyto`

Rule `pMEK_cyto` is a rate rule for species `pMEK_cyto`:

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\text{pMEK\_cyto} = \frac{1}{\text{numHillTau}} \cdot \Bigg(&\text{funcHillRafToMEK} \cdot \text{numHillMax} - [\text{pMEK\_cyto}] \\ &- \text{numMEKCytoToNucParam} \cdot [\text{pMEK\_cyto}] + \frac{1}{\text{numCytoToNucVolRatio}} \\ &\cdot \text{numMEKNucToCytoParam} \cdot [\text{pMEK\_nuc}]\Bigg)\end{aligned} \tag{10}$$

6.11 Rule `pERK_cyto`

Rule `pERK_cyto` is a rate rule for species `pERK_cyto`:

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\text{pERK\_cyto} = \frac{1}{\text{numHillTau}} \cdot \Bigg(&\text{funcHillMEKToERKCyto} \cdot \text{numHillMax} - [\text{pERK\_cyto}] \\ &- \text{numERKCytoToNucParam} \cdot [\text{pERK\_cyto}] + \frac{1}{\text{numCytoToNucVolRatio}} \\ &\cdot \text{numERKNucToCytoParam} \cdot [\text{pERK\_nuc}]\Bigg)\end{aligned} \tag{11}$$

6.12 Rule `pMEK_nuc`

Rule `pMEK_nuc` is a rate rule for species `pMEK_nuc`:

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\text{pMEK\_nuc} = \frac{1}{\text{numHillTau}} \cdot ([\text{pMEK\_nuc}] &- \text{numMEKNucToCytoParam} \cdot [\text{pMEK\_nuc}] \\ &+ \text{numCytoToNucVolRatio} \cdot \text{numMEKCytoToNucParam} \cdot [\text{pMEK\_cyto}])\end{aligned} \tag{12}$$

6.13 Rule pERK_nuc

Rule pERK_nuc is a rate rule for species pERK_nuc:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{pERK\_nuc} = \frac{1}{\mathrm{numHillTau}} \cdot ((\mathrm{funcHillMEKToERKNuc} - \mathrm{funcHillERKToERKNuc}) \cdot \mathrm{numHillMax} - [\mathrm{pERK\_nuc}] - \mathrm{numERKCytoToNucParam} \cdot [\mathrm{pERK\_nuc}] + \mathrm{numCytoToNucVolRatio} \cdot \mathrm{numERKNucToCytoParam} \cdot [\mathrm{pERK\_cyto}]) \tag{13}$$

7 Events

This is an overview of five events. Each event is initiated whenever its trigger condition switches from `false` to `true`. A delay function postpones the effects of an event to a later time point. At the time of execution, an event can assign values to species, parameters or compartments if these are not set to constant.

7.1 Event Position_0

Name Position 0

Trigger condition

$$\mathrm{numTissuePos} \geq 0 \tag{14}$$

Delay

$$0 \tag{15}$$

Assignments

$$\mathrm{Ca} = \mathrm{numCaInputBaseline} + \mathrm{numCaInputAmp} \cdot \frac{\mathrm{numTissuePos}}{5} \tag{16}$$

$$\mathrm{CaM\_memb} = \mathrm{numCaMInputBaseline} + \mathrm{numCaMInputAmp} \cdot \frac{\mathrm{numTissuePos} + 1}{2} \tag{17}$$

7.2 Event Position_1

Name Position 1

Trigger condition

$$\mathrm{numTissuePos} \geq 1 \tag{18}$$

Delay

$$0 \tag{19}$$

Assignment

$$\mathrm{CaM\_memb} = \mathrm{numCaMInputBaseline} + \mathrm{numCaMInputAmp} \cdot \exp(1 - \mathrm{numTissuePos}) \tag{20}$$

7.3 Event Position_5

Name Position 5

Trigger condition

$$\text{numTissuePos} \geq 5 \tag{21}$$

Delay

$$0 \tag{22}$$

Assignments

$$\text{Ca} = \text{numCaInputBaseline} + \text{numCaInputAmp} \cdot \frac{7 - \text{numTissuePos}}{2} \tag{23}$$

$$\text{CaM\_memb} = 0 \tag{24}$$

7.4 Event Total_Rafc_input_less_than_0

Name Total Rafc input less than 0

Trigger condition

$$\text{funcHillCaToRaf} - \text{funcHillCaMToRaf} - \text{funcHillERKToRaf} \leq 0 \tag{25}$$

Delay

$$0 \tag{26}$$

Assignment

$$\text{numTotalRafInputs} = 0 \tag{27}$$

7.5 Event Total_Raf_input_greater_than_0

Name Total Raf input greater than 0

Trigger condition

$$\text{funcHillCaToRaf} - \text{funcHillCaMToRaf} - \text{funcHillERKToRaf} > 0 \tag{28}$$

Delay

$$0 \tag{29}$$

Assignment

$$\text{numTotalRafInputs} = \text{funcHillCaToRaf} - \text{funcHillCaMToRaf} - \text{funcHillERKToRaf} \tag{30}$$

8 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.

8.1 Species pRaf_cyto

Name Rafc

Initial concentration $0.5\ \mathrm{mmol} \cdot \mathrm{l}^{-1}$

Involved in rule pRaf_cyto

One rule determines the species' quantity.

8.2 Species pMEK_cyto

Name MEKc

Initial concentration $0.8\ \mathrm{mmol} \cdot \mathrm{l}^{-1}$

Involved in rule pMEK_cyto

One rule determines the species' quantity.

8.3 Species pERK_cyto

Name ERKc

Initial concentration $0.7\ \mathrm{mmol} \cdot \mathrm{l}^{-1}$

Involved in rule pERK_cyto

One rule determines the species' quantity.

8.4 Species pMEK_nuc

Name MEKn

Initial concentration $0.4\ \mathrm{mmol} \cdot \mathrm{l}^{-1}$

Involved in rule pMEK_nuc

One rule determines the species' quantity.

8.5 Species pERK_nuc

Name ERKn

Initial concentration $0.2\ \mathrm{mmol} \cdot \mathrm{l}^{-1}$

Involved in rule pERK_nuc

One rule determines the species' quantity.

8.6 Species Ca

Name Ca

Initial concentration $0.7632\ \mathrm{mmol} \cdot \mathrm{l}^{-1}$

Involved in events Position_0, Position_5

two events influence the species' quantity.

8.7 Species CaM_memb

Name CaM

Initial concentration $0.72675\ \mathrm{mmol} \cdot \mathrm{l}^{-1}$

Involved in events Position_0, Position_1, Position_5

three events influence the species' quantity.

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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