## Changes made in Asthma\_V40\_M07

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## Summary

Changes:

Added a basal rate to all phosphorylation reactions.

Modified complex formation reactions: The rate based on Karagiannis was wrong, because of a misunderstanding of the moles vs. moles per liter. The papers of Chylek and Faeder supplied the clue.

Changed kinetic functions of transcription reactions, so that gene is always used (it was previously just a possible trigger).

Corrected all reversibility conditions, so that graphics and kinetics agree.

Corrected all transportation reactions, updating the reaction rates.

Checked for correct direction of all production/degradation reactions (not visible in graphics).

Added new production/degradation reactions where there were none.

Added new degradation reactions.

Result:

Model now integrates to 1e8 seconds in Copasi without integration errors or negative concentrations.

Data now include all of Parravicini and 3 steady-state conditions.

Optimization now succeeds, but only with maximum steady-state time of 1e5.

## Reversibility of reactions

re17

Drawn as reversible, marked as reversible in SBML, but kinetic law for irreversible used. Changed kinetic law to reversible.

c8 \* Metabolic\_Reaction\_2\_Modifiers\_\_irrev(s2805, k1m1, s1802, k1m2, s1998)

c8 \* Metabolic\_Reaction\_2\_Modifiers\_\_rev(s2805, k1m1, s1802, k1m2, s1998, k2, s2802)

re18

Drawn as reversible, marked as reversible in SBML, but kinetic law for irreversible used. Changed kinetic law to reversible.

c8 \* Metabolic\_Reaction\_0\_Modifier\_\_irrev(k1, s2802)

c8 \* Metabolic\_Reaction\_0\_Modifier\_\_rev(k1, s2805, k2, s2802)

re57

Drawn as irreversible, marked as irreversible in SBML, but kinetic law for reversible used. Changed graphic and SBML to reversible.

re78

Kinetics incorrect:

c8 \* Metabolic\_Reaction\_0\_Modifier\_\_irrev(k1, s2099)

should be

c8 \* Metabolic\_Reaction\_1\_Modifier\_\_irrev(k1, s2099, s3007)

s3007 is PI3K (complex) and is needed for measuring Akt-P in Parravicini Fig. 1f.

re83

Drawn as irreversible, marked as irreversible in SBML, but kinetic law for reversible used. Changed graphic and SBML to reversible.

re113

There was a mistake in the kinetics definition, where one substrate was also used as a modifier.

c8 \* Complex\_Formation\_2\_Substrates\_1\_Modifier\_\_rev(kon, s1892, s1941, s1892, koff, s1969)

s1892 appears twice. Should be param, substrate, substrate, modifier, param, product. That would mean that s1892 is both a substrate and a modifier. Changed to

c8 \* Complex\_Formation\_2\_Substrates\_\_rev(kon, s1892, s1941, koff, s1969)

re611, re612, re613

Drawn as irreversible, marked as irreversible in SBML, but kinetic law for reversible used. Changed graphic and SBML to reversible.

re625

Drawn as irreversible, marked as irreversible in SBML, but kinetic law for reversible used. Changed graphic and SBML to reversible.

re159, re160, re161, re162, re546, re547, re549, re550, re551, re560, re561, re562, re563, re564, re565, re608, re609, re610, re615, re616, re617, re629, re631, re632, re634, re635, re636, re637, re638, re639

In Copasi Check Model, these reaction cause warnings, because the reversibility of the function cannot be determined (unspecified reversibility). This cannot be changed in the SBML, but only in a cps file, so I will ignore the warnings. I don’t see any danger of confusion here, since these are reactions such as transcription where the reversibility is clear.

## Transport reactions

ABCB1 aka P-glycoprotein 1 (permeability glycoprotein, abbreviated as P-gp or Pgp) also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1) or cluster of differentiation 243 (CD243)

* Meng (2017) Extrapolation of Elementary Rate Constants of P-glycoprotein–Mediated Transport from MDCKII-hMDR1-NKI to Caco-2 Cells
* Tran (2005) The Elementary Mass Action Rate Constants of P-gp Transport for a Confluent Monolayer of MDCKII-hMDR1 Cells
* Mitra (2006) Role of ABCC1 in export of sphingosine-1-phosphate from mast cells
* Perloff (2009) BD Biosciences webinar. Slide 25: Efflux ratio from 2 to 18.

<https://www.ncbi.nlm.nih.gov/gene/4363>

* (Alangari (2010) Genomic and non-­genomic actions of glucocorticoids in asthma)

Based on Meng (2017) we will use a value of 10s-1 for all ABC transporters, and, as a very rough guess, for all transport reactions. If the reaction is reversible, the reverse will be set to 1s-1. We will also need concentrations for the transporters.

Transport reactions:

re53, re54, re55, re56, re59, re63, re64, re68, re83, re97, re98, re100, re104, re105, re108, re109, re110, re111, re123, re124, re125, re130, re131, re146, re167, re170, re176, re178, re411, re412, re415, re416, re555, re556, re557, re558, re559, re611, re612, re613, re641

Modifiers of transport reactions:

s2860 (ABCC1)

s2836 (ABCC2)

s2877 (ABCC3)

s2876 (ABCC4)

s2879 (ABCC6)

s2880 (ACCC10)

s2881 (ABCC11)

s2828 (ABCB1)

s2619 (ITPR1:IP3)

s2615 (ITPR2:IP3)

s2611 (ITPR3:IP3)

s2832 (mast cell degranulation)

s2143 (TRPC1)

re97 and re98 should be combined

re566, re567, re568, re569, re570, re571, re572, re573

Changed k1 to kdeg.

Introduced function Degradation for all degradation reactions.

## Phosphorylation reactions

Used estimate of re37, from Bouhaddou (2018) and Matallanas (2011), for all remaining phosphorylation reactions.

Added basal rate to all phosphorylation reactions so that LAT simulation starts at 1 instead of 0, in order to match Parravicini data (Fig. 1c).

## Fcer1

Changed FceR1 from constant to production/degradation so that Syk-P can degrade, in order to match Parravicini data (Fig. 1c).

## Production/degradation

Production/degradation reactions added for the following proteins:

s80 = INPP5D, set s78 to IC=0

s933 = IL4R, all complexes already have IC=0

s934 = JAK1

s935 = IL2RG

s936 = JAK3

s937 = STAT6, set s53, s54, s1371 IC=0

s944 = FES

s945 = IRS2

s999 = STAT3, set s1002, s1000, s1374 to IC=0

s1386 = JUN, set s1388 to IC=0

s1387 = FOS, set s1389 to IC=0

s1402 = ITPR3

s1403 = ITPR2

s1404 = ITPR1

s2041 = MAP2K2, s2949 already set to IC=0

s2095 = PLCG1

s2096 = VAV1

s2097 = TEC

s2098 = CALM1

s2115 = PAK1, set s2118 to IC=0

s2116 = PAK2, set s2119 to IC=0

s2117 = PAK3, set s2120 to IC=0

s2121 = MAP3K1, set s2122 to IC=0

s2123 = MAP2K4, set s2125 to IC=0

s2124 = MAP2K7, set s2126 to IC=0

s2127 = MAPK8, set s1383, s2130 to IC=0

s2128 = MAPK9, set s1384, s2131 to IC=0

s2129 = MAPK10, set s1385, s2132 to IC=0

s2135 = PRKCQ, complexes already set to IC=0

s2136 = CARD11, complexes already set to IC=0

s2137 = TRAF6, complexes already set to IC=0

s2139 = IRS1, set s2140 to IC=0

s2811 = RAF1, set s2812 to IC=0

s2813 = PLA2G4A, set s2814 to IC=0

s2823 = MAPK1, s1391, s2134, s2821 already set to IC=0

s2838 = TPSB2, set s2251 to IC=0

s2839 = TPSAB1, set s2253 to IC=0

s2870 = LPCAT2, set s2869 to IC=0

s2947 = MAPK3, s1390, s2133, s2822 already set to IC=0

s2948 = MAP2K1, s2820 already set to IC=0

Production/degradation reaction added for PIP2, IC set to 0 for PIP2 and PIP3.

Deleted (global) parameters N\_CARD11\_re138 and N\_CARD11\_re138, because they were not used.

Created a new (global) parameter kdegPDef (k degradation Protein Default) with value 1.9e-5 and used it for ALL protein degradation reactions (including production/degradation).

Created a new (global) parameter kdegRDef (k degradation RNA Default) with value 2.8e-5 and used it for ALL RNA degradation reactions (including production/degradation).

Created a new (global) parameter kdegSDef (k degradation Simple Molecule Default) with value 1e-5 (total guess!) and used it for ALL Simple Molecule degradation reactions (including production/degradation).

Production/degradation reactions for the following new proteins, and complex formation.

BCL10, MALT1, BCL10:MALT1 (complex)

CHUK, IKBKB, IKBKG, IKK (complex)

GRAP2, LCP2, GRAP2:LCP2 (complex)

HRAS, HRAS:GDP (complex)

RAC1, RAC1:GDP (complex)

IL13RA1, TYK2, IL13RA1:TYK2 (complex)

NFKBIA, NFKB1, RELA, IκBα:NFκB (complex)

TAB1, TAB2, TAK1, TAB1:TAB2:TAK1 (complex)

UBE2N, UBE2V1, UBE2N:UBE2V1 (complex)

Changed all kdeg parameters to global parameters (kdegPDef, kdegRDef and kdegSDef for protein/RNA/simple molecule default degradation).

Also reviewed all production/degradation reactions, because some of them had the wrong direction. Since the reaction is reversible, this is not visible in the top level of the diagram. Also reviewed all corresponding rates.

As a result, all problems with negative concentrations disappeared. Optimization now runs with very few integration errors. However, there are many cases where the gradient is very flat, and integration stops when the maximum number of iterations is reached. This is presumably because we are currently nor using enough data to determine an optimal value for most parameters.

Finally, we now have applied all relevant data from Parravicini, and also three steady-state definitions.