SBML Model Report

Model name: "Becker2010_EpoR_CoreModel"

May 6, 2016

1 General Overview

This is a document in SBML Level 2 Version 4 format. This model was created by the following three authors: Vijayalakshmi Chelliah[1], Marcel Schilling[2] and Verena Becker[3] at May 26th 2010 at 4:12 p. m. and last time modified at January 31st 2012 at 1:10 p. 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	3
species types	0	species	6
events	0	constraints	0
reactions	8	function definitions	0
global parameters	10	unit definitions	5
rules	2	initial assignments	0

Model Notes

This is the core model described in the article:
Covering a Broad Dynamic Range: Information Processing at the Erythropoietin Receptor

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Verena Becker, Marcel Schilling, Julie Bachmann, Ute Baumann, Andreas Raue, Thomas Maiwald, Jens Timmer and Ursula Klingmller; Science Published Online May 20, 2010; DOI: 10.1126/science.1184913 PMID: 20488988

Abstract:
Cell surface receptors convert extracellular cues into receptor activation, thereby triggering intracellular signaling networks and controlling cellular decisions. A major unresolved issue is the identification of receptor properties that critically determine processing of ligand-encoded information. We show by mathematical modeling of quantitative data and experimental validation that rapid ligand depletion and replenishment of cell surface receptor are characteristic features of the erythropoietin (Epo) receptor (EpoR). The amount of Epo-EpoR complexes and EpoR activation integrated over time corresponds linearly to ligand input, covering a broad range of ligand concentrations. This relation solely depends on EpoR turnover independent of ligand binding, suggesting an essential role of large intracellular receptor pools. These receptor properties enable the system to cope with basal and acute demand in the hematopoietic system.

SBML model exported from PottersWheel.

```
% PottersWheel model definition file

function m = BeckerSchilling2010_EpoR_CoreModel()

m             = pwGetEmptyModel();

%% Meta information

m.ID          = 'BeckerSchilling2010_EpoR_CoreModel';
m.name        = 'BeckerSchilling2010_EpoR_CoreModel';
m.description = 'BeckerSchilling2010_EpoR_CoreModel';
m.authors     = {'Verena Becker',' Marcel Schilling'};
m.dates       = {'2010'};
m.type        = 'PW-2-0-42';

%% X: Dynamic variables
% m = pwAddX(m, ID, startValue, type, minValue, maxValue, unit, compartment, name, descr

m = pwAddX(m, 'EpoR'     ,     516, 'fix'   ,    0, 10000,   [], 'cell', []  , []  , []
m = pwAddX(m, 'Epo'      , 2030.19, 'global', 1890,  2310,   [], 'cell', []  , []  , []
m = pwAddX(m, 'Epo_EpoR' ,       0, 'fix'   ,    0, 10000,   [], 'cell', []  , []  , []
m = pwAddX(m, 'Epo_EpoRi',       0, 'fix'   ,    0, 10000,   [], 'cell', []  , []  , []
m = pwAddX(m, 'dEpoi'    ,       0, 'fix'   ,    0, 10000,   [], 'cell', []  , []  , []
m = pwAddX(m, 'dEpoe'    ,       0, 'fix'   ,    0, 10000,   [], 'cell', []  , []  , []


%% R: Reactions
% m = pwAddR(m, reactants, products, modifiers, type, options, rateSignature, parameters
```

```
m = pwAddR(m, {            }, {'EpoR'      }, {  }, 'C' , [] , 'k1*k2', {'kt','Bmax'}, []
m = pwAddR(m, {'EpoR'      }, {            }, {  }, 'MA', [] , []     , {'kt'       }, []
m = pwAddR(m, {'Epo','EpoR'}, {'Epo_EpoR'  }, {  }, 'MA', [] , []     , {'kon'      }, []
m = pwAddR(m, {'Epo_EpoR'  }, {'Epo','EpoR'}, {  }, 'MA', [] , []     , {'koff'     }, []
m = pwAddR(m, {'Epo_EpoR'  }, {'Epo_EpoRi' }, {  }, 'MA', [] , []     , {'ke'       }, []
m = pwAddR(m, {'Epo_EpoRi' }, {'Epo','EpoR'}, {  }, 'MA', [] , []     , {'kex'      }, []
m = pwAddR(m, {'Epo_EpoRi' }, {'dEpoi'     }, {  }, 'MA', [] , []     , {'kdi'      }, []
m = pwAddR(m, {'Epo_EpoRi' }, {'dEpoe'     }, {  }, 'MA', [] , []     , {'kde'      }, []
```

```
%% C: Compartments
% m = pwAddC(m, ID, size,  outside, spatialDimensions, name, unit, constant)

m = pwAddC(m, 'cell', 1);
```

```
%% K: Dynamical parameters
% m = pwAddK(m, ID, value, type, minValue, maxValue, unit, name, description)

m = pwAddK(m, 'kt'  , 0.0329366 , 'global', 1e-007, 1000);
m = pwAddK(m, 'Bmax', 516       , 'fix'   , 492   , 540 );
m = pwAddK(m, 'kon' , 0.00010496, 'global', 1e-007, 1000);
m = pwAddK(m, 'koff', 0.0172135 , 'global', 1e-007, 1000);
m = pwAddK(m, 'ke'  , 0.0748267 , 'global', 1e-007, 1000);
m = pwAddK(m, 'kex' , 0.00993805, 'global', 1e-007, 1000);
m = pwAddK(m, 'kdi' , 0.00317871, 'global', 1e-007, 1000);
m = pwAddK(m, 'kde' , 0.0164042 , 'global', 1e-007, 1000);
```

```
%% Default sampling time points
m.t = 0:3:99;
```

```
%% Y: Observables
% m = pwAddY(m, rhs, ID, scalingParameter, errorModel, noiseType, unit, name, description

m = pwAddY(m, 'Epo + dEpoe'      , 'Epo_extracellular_obs');
m = pwAddY(m, 'Epo_EpoR'         , 'Epo_cellsurface_obs'  );
m = pwAddY(m, 'Epo_EpoRi + dEpoi', 'Epo_intracellular_obs');
```

```
%% S: Scaling parameters
% m = pwAddS(m, ID, value, type, minValue, maxValue, unit, name, description)

m = pwAddS(m, 'scale_Epo_extracellular_obs', 1, 'fix', 0, 100);
m = pwAddS(m, 'scale_Epo_cellsurface_obs'  , 1, 'fix', 0, 100);
m = pwAddS(m, 'scale_Epo_intracellular_obs', 1, 'fix', 0, 100);


%% Designer properties (do not modify)
m.designerPropsM = [1 1 1 0 0 0 400 250 600 400 1 1 1 0 0 0 0];
```


2 Unit Definitions

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

2.1 Unit `time`

Name minute

Definition 60 s

2.2 Unit `per_minute`

Definition $(60\,\mathrm{s})^{-1}$

2.3 Unit `substance`

Name picomole

Definition $10^{-12}\,\mathrm{mol}$

2.4 Unit `pM`

Definition $10^{-12}\,\mathrm{mol}\cdot 1^{-1}$

2.5 Unit per_minute_per_pM

Definition $(60\ \mathrm{s})^{-1} \cdot \left(10^{-12}\ \mathrm{mol}\right)^{-1} \cdot 1$

2.6 Unit volume

Notes Litre is the predefined SBML unit for volume.

Definition l

2.7 Unit area

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

Definition m^2

2.8 Unit length

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

Definition m

3 Compartments

This model contains three compartments.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
medium	medium	0000290	3	1	litre	☑	
cellsurface	cellsurface	0000290	3	1	litre	☑	
cell	cell	0000290	3	1	litre	☑	

3.1 Compartment medium

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

Name medium

SBO:0000290 physical compartment

3.2 Compartment cellsurface

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

Name cellsurface

SBO:0000290 physical compartment

3.3 Compartment `cell`

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

Name cell

SBO:0000290 physical compartment

4 Species

This model contains six species. 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
EpoR	EpoR	cellsurface	10^{-12} mol · l^{-1}	⊟	⊟
Epo	Epo	medium	10^{-12} mol · l^{-1}	⊟	⊟
Epo_EpoR	Epo_EpoR	cellsurface	10^{-12} mol · l^{-1}	⊟	⊟
Epo_EpoRi	Epo_EpoRi	cell	10^{-12} mol · l^{-1}	⊟	⊟
dEpoi	dEpoi	cell	10^{-12} mol · l^{-1}	⊟	⊟
dEpoe	dEpoe	medium	10^{-12} mol · l^{-1}	⊟	⊟

5 Parameters

This model contains ten global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
kt		0000256	0.033	$(60\ \mathrm{s})^{-1}$	☑
Bmax		0000256	516.000	$10^{-12}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$	☑
kon		0000341	$1.0496\cdot10^{-4}$	$(60\ \mathrm{s})^{-1}\cdot\left(10^{-12}\ \mathrm{mol}\right)^{-1}\cdot\mathrm{l}$	☑
koff		0000338	0.017	$(60\ \mathrm{s})^{-1}$	☑
ke		0000256	0.075	$(60\ \mathrm{s})^{-1}$	☑
kex		0000256	0.010	$(60\ \mathrm{s})^{-1}$	☑
kdi		0000356	0.003	$(60\ \mathrm{s})^{-1}$	☑
kde		0000356	0.016	$(60\ \mathrm{s})^{-1}$	☑
Epo_medium	Epo_medium		0.000		⊟
Epo_cells	Epo_cells		0.000		⊟

6 Rules

This is an overview of two rules.

6.1 Rule Epo_medium

Rule Epo_medium is an assignment rule for parameter Epo_medium:

$$\mathrm{Epo\_medium} = [\mathrm{Epo}] + [\mathrm{dEpoe}] \tag{1}$$

Derived unit $10^{-12}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

6.2 Rule Epo_cells

Rule Epo_cells is an assignment rule for parameter Epo_cells:

$$\mathrm{Epo\_cells} = [\mathrm{Epo\_EpoRi}] + [\mathrm{dEpoi}] \tag{2}$$

Derived unit $10^{-12}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

7 Reactions

This model contains eight 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 5: Overview of all reactions

№	Id	Name	Reaction Equation	SBO
1	reaction_1		$\emptyset \longrightarrow \mathrm{EpoR}$	0000176
2	reaction_2		$\mathrm{EpoR} \longrightarrow \emptyset$	0000179
3	reaction_3		$\mathrm{Epo} + \mathrm{EpoR} \longrightarrow \mathrm{Epo\_EpoR}$	0000177
4	reaction_4		$\mathrm{Epo\_EpoR} \longrightarrow \mathrm{Epo} + \mathrm{EpoR}$	0000180
5	reaction_5		$\mathrm{Epo\_EpoR} \longrightarrow \mathrm{Epo\_EpoRi}$	0000185
6	reaction_6		$\mathrm{Epo\_EpoRi} \longrightarrow \mathrm{Epo} + \mathrm{EpoR}$	0000180
7	reaction_7		$\mathrm{Epo\_EpoRi} \longrightarrow \mathrm{dEpoi}$	0000179
8	reaction_8		$\mathrm{Epo\_EpoRi} \longrightarrow \mathrm{dEpoe}$	0000179

7.1 Reaction `reaction_1`

This is an irreversible reaction of no reactant forming one product.

SBO:0000176 biochemical reaction

Reaction equation

$$\emptyset \longrightarrow \mathrm{EpoR} \tag{3}$$

Product

Table 6: Properties of each product.

Id	Name	SBO
EpoR	EpoR	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot 10^{-12}\ \mathrm{mol}$

$$v_1 = \mathrm{kt} \cdot \mathrm{Bmax} \cdot \mathrm{vol}\,(\mathrm{cell}) \tag{4}$$

7.2 Reaction `reaction_2`

This is an irreversible reaction of one reactant forming no product.

SBO:0000179 degradation

Reaction equation

$$\mathrm{EpoR} \longrightarrow \emptyset \tag{5}$$

Reactant

Table 7: Properties of each reactant.

Id	Name	SBO
EpoR	EpoR	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot 10^{-12}\ \mathrm{mol}$

$$v_2 = \mathrm{kt} \cdot [\mathrm{EpoR}] \cdot \mathrm{vol}(\mathrm{cell}) \tag{6}$$

7.3 Reaction `reaction_3`

This is an irreversible reaction of two reactants forming one product.

SBO:0000177 non-covalent binding

Reaction equation

$$\mathrm{Epo} + \mathrm{EpoR} \longrightarrow \mathrm{Epo\_EpoR} \tag{7}$$

Reactants

Table 8: Properties of each reactant.

Id	Name	SBO
Epo	Epo	
EpoR	EpoR	

Product

Table 9: Properties of each product.

Id	Name	SBO
Epo_EpoR	Epo_EpoR	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot 10^{-12}\ \mathrm{mol}$

$$v_3 = \mathrm{kon} \cdot [\mathrm{Epo}] \cdot [\mathrm{EpoR}] \cdot \mathrm{vol}(\mathrm{cell}) \tag{8}$$

7.4 Reaction `reaction_4`

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

SBO:0000180 dissociation

Reaction equation

$$\mathrm{Epo\_EpoR} \longrightarrow \mathrm{Epo} + \mathrm{EpoR} \tag{9}$$

Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
Epo_EpoR	Epo_EpoR	

Products

Table 11: Properties of each product.

Id	Name	SBO
Epo	Epo	
EpoR	EpoR	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot 10^{-12}\ \mathrm{mol}$

$$v_4 = \mathrm{koff} \cdot [\mathrm{Epo\_EpoR}] \cdot \mathrm{vol}(\mathrm{cell}) \tag{10}$$

7.5 Reaction reaction_5

This is an irreversible reaction of one reactant forming one product.

SBO:0000185 transport reaction

Reaction equation

$$\mathrm{Epo\_EpoR} \longrightarrow \mathrm{Epo\_EpoRi} \tag{11}$$

Reactant

Table 12: Properties of each reactant.

Id	Name	SBO
Epo_EpoR	Epo_EpoR	

Product

Table 13: Properties of each product.

Id	Name	SBO
Epo_EpoRi	Epo_EpoRi	

Id	Name	SBO

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot 10^{-12}\ \mathrm{mol}$

$$v_5 = \mathrm{ke} \cdot [\mathrm{Epo\_EpoR}] \cdot \mathrm{vol}\,(\mathrm{cell}) \tag{12}$$

7.6 Reaction `reaction_6`

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

SBO:0000180 dissociation

Reaction equation

$$\mathrm{Epo\_EpoRi} \longrightarrow \mathrm{Epo} + \mathrm{EpoR} \tag{13}$$

Reactant

Table 14: Properties of each reactant.

Id	Name	SBO
`Epo_EpoRi`	Epo_EpoRi	

Products

Table 15: Properties of each product.

Id	Name	SBO
`Epo`	Epo	
`EpoR`	EpoR	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot 10^{-12}\ \mathrm{mol}$

$$v_6 = \mathrm{kex} \cdot [\mathrm{Epo\_EpoRi}] \cdot \mathrm{vol}\,(\mathrm{cell}) \tag{14}$$

7.7 Reaction `reaction_7`

This is an irreversible reaction of one reactant forming one product.

SBO:0000179 degradation

Reaction equation

$$\text{Epo\_EpoRi} \longrightarrow \text{dEpoi} \tag{15}$$

Reactant

Table 16: Properties of each reactant.

Id	Name	SBO
Epo_EpoRi	Epo_EpoRi	

Product

Table 17: Properties of each product.

Id	Name	SBO
dEpoi	dEpoi	

Kinetic Law

Derived unit $(60\ \text{s})^{-1} \cdot 10^{-12}\ \text{mol}$

$$v_7 = \text{kdi} \cdot [\text{Epo\_EpoRi}] \cdot \text{vol}(\text{cell}) \tag{16}$$

7.8 Reaction reaction_8

This is an irreversible reaction of one reactant forming one product.

SBO:0000179 degradation

Reaction equation

$$\text{Epo\_EpoRi} \longrightarrow \text{dEpoe} \tag{17}$$

Reactant

Table 18: Properties of each reactant.

Id	Name	SBO
Epo_EpoRi	Epo_EpoRi	

Product

Table 19: Properties of each product.

Id	Name	SBO
dEpoe	dEpoe	

Kinetic Law

Derived unit $(60\ \mathrm{s})^{-1} \cdot 10^{-12}\ \mathrm{mol}$

$$v_8 = \mathrm{kde} \cdot [\mathrm{Epo\_EpoRi}] \cdot \mathrm{vol}\,(\mathrm{cell}) \tag{18}$$

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 EpoR

Name EpoR

SBO:0000244 receptor

Initial concentration $516\ 10^{-12}\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

This species takes part in five reactions (as a reactant in reaction_2, reaction_3 and as a product in reaction_1, reaction_4, reaction_6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{EpoR} = v_1 + v_4 + v_6 - v_2 - v_3 \tag{19}$$

8.2 Species Epo

Name Epo

SBO:0000280 ligand

Initial concentration $2030.19\ 10^{-12}\ \mathrm{mol} \cdot \mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in reaction_3 and as a product in reaction_4, reaction_6).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Epo} = v_4 + v_6 - v_3 \tag{20}$$

8.3 Species Epo_EpoR

Name Epo_EpoR

SBO:0000297 protein complex

Initial concentration $0\ 10^{-12}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in three reactions (as a reactant in reaction_4, reaction_5 and as a product in reaction_3).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Epo\_EpoR} = v_3 - v_4 - v_5 \tag{21}$$

8.4 Species Epo_EpoRi

Name Epo_EpoRi

SBO:0000297 protein complex

Initial concentration $0\ 10^{-12}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in four reactions (as a reactant in reaction_6, reaction_7, reaction_8 and as a product in reaction_5).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{Epo\_EpoRi} = v_5 - v_6 - v_7 - v_8 \tag{22}$$

8.5 Species dEpoi

Name dEpoi

SBO:0000291 empty set

Initial concentration $0\ 10^{-12}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in one reaction (as a product in reaction_7).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{dEpoi} = v_7 \tag{23}$$

8.6 Species dEpoe

Name dEpoe

SBO:0000291 empty set

Initial concentration $0\ 10^{-12}\ \mathrm{mol}\cdot\mathrm{l}^{-1}$

This species takes part in one reaction (as a product in reaction_8).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{dEpoe} = v_8 \tag{24}$$

A Glossary of Systems Biology Ontology Terms

SBO:0000176 biochemical reaction: An event involving one or more chemical entities that modifies the electrochemical structure of at least one of the participants.

SBO:0000177 non-covalent binding: Interaction between several biochemical entities that results in the formation of a non-covalent comple

SBO:0000179 degradation: Complete disappearance of a physical entity

SBO:0000180 dissociation: Transformation of a non-covalent complex that results in the formation of several independent biochemical entitie

SBO:0000185 transport reaction: Movement of a physical entity without modification of the structure of the entity

SBO:0000244 receptor: Participating entity that binds to a specific physical entity and initiates the response to that physical entity.The original concept of the receptor was introduced independently at the end of the 19th century by John Newport Langley (1852-1925) and Paul Ehrlich (1854-1915). Langley JN.On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards the reaction of striated muscle to nicotine and to curari. J Physiol. 1905 Dec 30;33(4-5):374-413

SBO:0000256 biochemical parameter: Parameter that depends on the biochemical properties of a system

SBO:0000280 ligand: In biochemistry, a ligand is an effector, a physical entity that binds to a site on a receptor's surface by intermolecular forces

SBO:0000290 physical compartment: Specific location of space, that can be bounded or not. A physical compartment can have 1, 2 or 3 dimensions

SBO:0000291 empty set: Entity defined by the absence of any actual object. An empty set is often used to represent the source of a creation process or the result of a degradation process.

SBO:0000297 protein complex: Macromolecular complex containing one or more polypeptide chains possibly associated with simple chemicals. CHEBI:3608

SBO:0000338 dissociation rate constant: Rate with which a complex dissociates into its components

SBO:0000341 association rate constant: Rate with which components associate into a complex

SBO:0000356 decay constant: Kinetic constant characterising a mono-exponential decay. It is the inverse of the mean lifetime of the continuant being decayed. Its unit is"per tim".

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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