# **SBML Model Report**

# Model name: "Grigolon2018 - Feedback Loop in ARF and IAA Response"



October 12, 2018

# 1 General Overview

This is a document in SBML Level 2 Version 3 format. This model was created by the following three authors: Silvia Grigolon<sup>1</sup>, Olivier Martin<sup>2</sup> and Barbara Bravi<sup>3</sup> at June seventh 2017 at 10:42 a.m. Table 1 provides 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	1
species types	0	species	11
events	0	constraints	0
reactions	16	function definitions	0
global parameters	19	unit definitions	0
rules	0	initial assignments	0

#### **Model Notes**

Grigolon2018 - Feedback Loop in ARF and IAAResponse

<sup>&</sup>lt;sup>1</sup>The Francis Crick Institute, London, silvia.grigolon@gmail.com

<sup>&</sup>lt;sup>2</sup>GQE-Le Moulon, INRA, Univ. Paris-Sud, CNRS, AgroParisTech, Universit Paris-Saclay, olivier.martin@moulon.inra.fr

<sup>&</sup>lt;sup>3</sup>Institute of Theoretical Physics, cole Polytechnique Fdrale de Lausanne, barbara.bravi@epfl.ch

This model is described in the article:Responses to auxin signals: an operating principle for dynamical sensitivity yet high resilience. Grigolon S, Bravi B, Martin OC.R Soc Open Sci 2018 Jan; 5(1): 172098

Abstract:

Plants depend on the signalling of the phytohormone auxin for their development and for responding to environmental perturbations. The associated biomolecular signalling network involves a negative feedback on Aux/IAA proteins which mediate the influence of auxin (the signal) on the auxin response factor (ARF) transcription factors (the drivers of the response). To probe the role of this feedback, we consider alternative in silico signalling networks implementing different operating principles. By a comparative analysis, we find that the presence of a negative feedback allows the system to have a far larger sensitivity in its dynamical response to auxin and that this sensitivity does not prevent the system from being highly resilient. Given this insight, we build a new biomolecular signalling model for quantitatively describing such Aux/IAA and ARF responses.

This model is hosted on BioModels Database and identified by: MODEL1706070000.

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

To the extent possible under law, all copyright and related or neighbouring rights to this encoded model have been dedicated to the public domain worldwide. Please refer to CCO Public Domain Dedication for more information.

#### 2 Unit Definitions

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

#### 2.1 Unit substance

**Notes** Mole is the predefined SBML unit for substance.

**Definition** mol

#### 2.2 Unit volume

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

**Definition** 1

#### 2.3 Unit area

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

**Definition** m<sup>2</sup>

# 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 Compartment

This model contains one compartment.

Table 2: Properties of all compartments.

Id	Name	SBO	Spatial Dimensions	Size	Unit	Constant	Outside
Cell	Cell		3	1	litre	Ø	

# 3.1 Compartment Cell

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

Name Cell

4

# 4 Species

This model contains eleven species. The boundary condition of one of these species is set to true so that this species' amount cannot be changed by any reaction. Section 7 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 Condi- tion
aux	aux	Cell	$\text{mol} \cdot l^{-1}$		
IAAm	IAAm	Cell	$\operatorname{mol} \cdot 1^{-1}$	$\Box$	
IAAp	IAAp	Cell	$\operatorname{mol} \cdot 1^{-1}$	$\Box$	
ARF	ARF	Cell	$\operatorname{mol} \cdot 1^{-1}$	$\Box$	
null	null	Cell	$\operatorname{mol} \cdot 1^{-1}$		
ARFIAA	ARFIAA	Cell	$\text{mol} \cdot 1^{-1}$		
ARF2	ARF2	Cell	$\text{mol} \cdot 1^{-1}$		
auxTIR1	auxTIR1	Cell	$\operatorname{mol} \cdot 1^{-1}$	$\Box$	
auxTIR1IAA	auxTIR1IAA	Cell	$\operatorname{mol} \cdot 1^{-1}$	$\Box$	
TIR1	TIR1	Cell	$\text{mol} \cdot l^{-1}$	$\Box$	
IAAstar	IAAstar	Cell	$\text{mol} \cdot l^{-1}$	$\Box$	$\Box$

# **5 Parameters**

This model contains 19 global parameters.

Table 4: Properties of each parameter.

Id	Name	SBO	Value	Unit	Constant
Sauxin	Sauxin		0.020		$\checkmark$
muaux	muaux		0.100		$\overline{\mathbf{Z}}$
lambda1	lambda1		0.480		$\overline{\mathbf{Z}}$
thetaARF	thetaARF		100.000		$\overline{\mathbf{Z}}$
thetaARF2	thetaARF2		100.000		$\overline{\mathbf{Z}}$
thetaARFIAA	thetaARFIAA		100.000		$\overline{\mathbf{Z}}$
muIAAm	muIAAm		0.003		$\overline{\mathbf{Z}}$
muIAA	muIAA		0.003		$\overline{\mathbf{Z}}$
delta	delta		4.000		$\overline{\mathbf{Z}}$
qa	qa		0.500		$\overline{\mathbf{Z}}$
qd	qd		0.440		$\overline{\mathbf{Z}}$
pa	pa		1.000		$\overline{\mathbf{Z}}$
pd	pd		0.072		$\overline{\mathbf{Z}}$
ka	ka		$8.2 \cdot 10^{-4}$		$\overline{\mathbf{Z}}$
kd	kd		0.330		$\overline{\mathbf{Z}}$
la	la		5.750		$\overline{\mathbf{Z}}$
ld	ld		0.045		$\overline{\mathbf{Z}}$
lm	lm		0.900		$\overline{\mathbf{Z}}$
muIAAstar	muIAAstar		0.100		<u> </u>

# 6 Reactions

This model contains 16 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

N⁰	Id	Name	Reaction Equation	SBO
1	auxin-	auxin_production	null <del>←</del> aux	
	$\_\mathtt{production}$			
2	auxin-	auxin_degradation	aux <del>←</del> null	
	$\_\mathtt{degradation}$			
3	$\mathtt{mRNA\_production}$	mRNA_production	null ARF, ARF2, ARFIAA IAAm	
4	mRNA-	mRNA_degradation	IAAm <del>←</del> null	
	$\_$ degradation	· ·		
5	${\tt IAA\_degradation}$	IAA_degradation	$IAAp \Longrightarrow null$	
6	mRNA-	mRNA_translation	$IAAm \rightleftharpoons IAAm + IAAp$	
	$_{ extsf{-}}translation$			
7	$\mathtt{ARF2\_formation}$	ARF2_formation	$2 ARF \Longrightarrow ARF2$	
8	ARF2-	ARF2_dissociation	$ARF2 \Longrightarrow 2ARF$	
	$\_$ dissociation			
9	ARFIAA-	ARFIAA_formation	$ARF + IAAp \Longrightarrow ARFIAA$	
4.0	_formation			
10	ARFIAA-	ARFIAA_dissociation	$ARFIAA \Longrightarrow ARF + IAAp$	
	_dissociation	TITO 1 C	TVD4	
11	auxTIR1-	auxTIR1_formation	$aux + TIR1 \Longrightarrow auxTIR1$	
10	_formation	TID 1 1'''	TID1	
12	auxTIR1-	auxTIR1_dissociation	$auxTIR1 \Longrightarrow aux + TIR1$	
	$\_\mathtt{dissociation}$			

N⁰	Id	Name	Reaction Equation	SBO
13	auxTIR1IAA- _formation	auxTIR1IAA_formation	$auxTIR1 + IAAp \Longrightarrow auxTIR1IAA$	
14	auxTIR1IAA- _dissociation	auxTIR1IAA_dissociation	$auxTIR1IAA \Longrightarrow auxTIR1 + IAAp$	
15	IAA- _ubiquitination	IAA_ubiquitination	$auxTIR1IAA \Longrightarrow auxTIR1 + IAAstar$	
16	IAAstar- _degradation	IAAstar_degradation	IAAstar <del>←</del> null	

# **6.1 Reaction** auxin\_production

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

Name auxin\_production

# **Reaction equation**

$$null \Longrightarrow aux$$
 (1)

#### Reactant

Table 6: Properties of each reactant.

Id	Name	SBO
null	null	

#### **Product**

Table 7: Properties of each product.

Id	Name	SBO
aux	aux	

#### **Kinetic Law**

**Derived unit** not available

$$v_1 =$$
Sauxin (2)

# **6.2 Reaction** auxin\_degradation

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

Name auxin\_degradation

#### **Reaction equation**

$$aux \rightleftharpoons null$$
 (3)

#### Reactant

Table 8: Properties of each reactant.

Id	Name	SBO
aux	aux	

Table 9: Properties of each product.

Id	Name	SBO
null	null	

#### **Kinetic Law**

Derived unit contains undeclared units

$$v_2 = [aux] \cdot muaux \tag{4}$$

# **6.3 Reaction** mRNA\_production

This is a reversible reaction of one reactant forming one product influenced by three modifiers.

Name mRNA\_production

# **Reaction equation**

$$null \xrightarrow{ARF, ARF2, ARFIAA} IAAm$$
 (5)

#### Reactant

Table 10: Properties of each reactant.

Id	Name	SBO
null	null	

#### **Modifiers**

Table 11: Properties of each modifier.

Id	Name	SBO
ARF	ARF	
ARF2	ARF2	
ARFIAA	ARFIAA	

Table 12: Properties of each product.

Id	Name	SBO
IAAm	IAAm	

#### **Kinetic Law**

Derived unit contains undeclared units

$$v_{3} = [ARF] \cdot lambda1 \cdot \left(thetaARF \cdot \left([ARF] \cdot thetaARF^{-1} + [ARF2] \cdot thetaARF2^{-1} + [ARFIAA] \cdot thetaARFIAA^{-1} + 1\right)\right)^{-1}$$
 (6)

# **6.4 Reaction** mRNA\_degradation

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

Name mRNA\_degradation

# **Reaction equation**

$$IAAm \rightleftharpoons null \tag{7}$$

#### Reactant

Table 13: Properties of each reactant.

Id	Name	SBO
IAAm	IAAm	

Table 14: Properties of each product.

Id	Name	SBO
null	null	

# **Kinetic Law**

**Derived unit** contains undeclared units

$$v_4 = [IAAm] \cdot muIAAm \tag{8}$$

# **6.5 Reaction** IAA\_degradation

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

Name IAA\_degradation

# **Reaction equation**

$$IAAp \rightleftharpoons null \tag{9}$$

#### Reactant

Table 15: Properties of each reactant.

Id	Name	SBO
IAAp	IAAp	

#### **Product**

Table 16: Properties of each product.

Id	Name	SBO
null	null	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_5 = [IAAp] \cdot muIAA \tag{10}$$

# **6.6 Reaction** mRNA\_translation

This is a reversible reaction of one reactant forming two products.

Name mRNA\_translation

#### **Reaction equation**

$$IAAm \rightleftharpoons IAAm + IAAp \tag{11}$$

#### Reactant

Table 17: Properties of each reactant.

Id	Name	SBO
IAAm	IAAm	

#### **Products**

Table 18: Properties of each product.

Id	Name	SBO
IAAm	IAAm	
IAAp	IAAp	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_6 = \text{delta} \cdot [\text{IAAm}]$$
 (12)

# **6.7 Reaction** ARF2\_formation

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

Name ARF2\_formation

# **Reaction equation**

$$2 ARF \Longrightarrow ARF2$$
 (13)

# Reactant

Table 19: Properties of each reactant.

Id	Name	SBO
ARF	ARF	

#### **Product**

Table 20: Properties of each product.

Id	Name	SBO
ARF2	ARF2	

#### **Kinetic Law**

Derived unit contains undeclared units

$$v_7 = [ARF]^2 \cdot qa \tag{14}$$

# **6.8 Reaction** ARF2\_dissociation

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

Name ARF2\_dissociation

# **Reaction equation**

$$ARF2 \rightleftharpoons 2ARF$$
 (15)

#### Reactant

Table 21: Properties of each reactant.

Id	Name	SBO
ARF2	ARF2	

#### **Product**

Table 22: Properties of each product.

Id	Name	SBO
ARF	ARF	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_8 = [ARF2] \cdot qd \tag{16}$$

#### 6.9 Reaction ARFIAA\_formation

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

Name ARFIAA\_formation

# **Reaction equation**

$$ARF + IAAp \Longrightarrow ARFIAA \tag{17}$$

#### **Reactants**

Table 23: Properties of each reactant.

Id	Name	SBO
ARF	ARF	
IAAp	IAAp	

#### **Product**

Table 24: Properties of each product.

Id	Name	SBO
ARFIAA	ARFIAA	

# **Kinetic Law**

Derived unit contains undeclared units

$$v_9 = [ARF] \cdot [IAAp] \cdot pa \tag{18}$$

# **6.10 Reaction** ARFIAA\_dissociation

This is a reversible reaction of one reactant forming two products.

Name ARFIAA\_dissociation

# **Reaction equation**

$$ARFIAA \Longrightarrow ARF + IAAp \tag{19}$$

#### Reactant

Table 25: Properties of each reactant.

Id	Name	SBO
ARFIAA	ARFIAA	

#### **Products**

Table 26: Properties of each product.

Id	Name	SBO
ARF	ARF	
IAAp	IAAp	

#### **Kinetic Law**

Derived unit contains undeclared units

$$v_{10} = [ARFIAA] \cdot pd \tag{20}$$

#### **6.11 Reaction** auxTIR1\_formation

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

Name auxTIR1\_formation

# **Reaction equation**

$$aux + TIR1 \Longrightarrow auxTIR1$$
 (21)

#### **Reactants**

Table 27: Properties of each reactant.

Id	Name	SBO
aux	aux	
TIR1	TIR1	

Table 28: Properties of each product.

Id	Name	SBO
auxTIR1	auxTIR1	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{11} = [aux] \cdot ka \cdot [TIR1] \tag{22}$$

# **6.12 Reaction** auxTIR1\_dissociation

This is a reversible reaction of one reactant forming two products.

Name auxTIR1\_dissociation

# **Reaction equation**

$$auxTIR1 \Longrightarrow aux + TIR1 \tag{23}$$

#### Reactant

Table 29: Properties of each reactant.

Id	Name	SBO
auxTIR1	auxTIR1	

# **Products**

Table 30: Properties of each product.

Id	Name	SBO
aux	aux	
TIR1	TIR1	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{12} = [\text{auxTIR1}] \cdot \text{kd} \tag{24}$$

# **6.13 Reaction** auxTIR1IAA\_formation

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

Name auxTIR1IAA\_formation

# **Reaction equation**

$$auxTIR1 + IAAp \Longrightarrow auxTIR1IAA$$
 (25)

#### **Reactants**

Table 31: Properties of each reactant.

Id	Name	SBO
auxTIR1	auxTIR1	
IAAp	IAAp	

#### **Product**

Table 32: Properties of each product.

Id	Name	SBO
auxTIR1IAA	auxTIR1IAA	

# **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{13} = [auxTIR1] \cdot [IAAp] \cdot la \tag{26}$$

#### **6.14 Reaction** auxTIR1IAA\_dissociation

This is a reversible reaction of one reactant forming two products.

Name auxTIR1IAA\_dissociation

# **Reaction equation**

$$auxTIR1IAA \Longrightarrow auxTIR1 + IAAp \tag{27}$$

#### Reactant

Table 33: Properties of each reactant.

Id	Name	SBO
auxTIR1IAA	auxTIR1IAA	

#### **Products**

Table 34: Properties of each product.

Id	Name	SBO
auxTIR1	auxTIR1	
IAAp	IAAp	

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{14} = [auxTIR1IAA] \cdot ld \tag{28}$$

# **6.15 Reaction** IAA\_ubiquitination

This is a reversible reaction of one reactant forming two products.

Name IAA\_ubiquitination

# **Reaction equation**

$$auxTIR1IAA \Longrightarrow auxTIR1 + IAAstar$$
 (29)

#### Reactant

Table 35: Properties of each reactant.

Id	Name	SBO
auxTIR1IAA	auxTIR1IAA	

#### **Products**

Table 36: Properties of each product.

Id	Name	SBO
auxTIR1 IAAstar		

#### **Kinetic Law**

**Derived unit** contains undeclared units

$$v_{15} = [\text{auxTIR1IAA}] \cdot \text{lm} \tag{30}$$

# **6.16 Reaction** IAAstar\_degradation

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

Name IAAstar\_degradation

# **Reaction equation**

$$IAAstar \rightleftharpoons null \tag{31}$$

#### Reactant

Table 37: Properties of each reactant.

Id	Name	SBO
IAAstar	IAAstar	

#### **Product**

Table 38: Properties of each product.

Id	Name	SBO
null	null	

#### **Kinetic Law**

Derived unit contains undeclared units

$$v_{16} = [IAAstar] \cdot muIAAstar$$
 (32)

# 7 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.

#### 7.1 Species aux

Name aux

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

This species takes part in four reactions (as a reactant in auxin\_degradation, auxTIR1-\_formation and as a product in auxin\_production, auxTIR1\_dissociation).

$$\frac{d}{dt}aux = |v_1| + |v_{12}| - |v_2| - |v_{11}| \tag{33}$$

# 7.2 Species IAAm

Name IAAm

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

This species takes part in four reactions (as a reactant in mRNA\_degradation, mRNA\_translation and as a product in mRNA\_production, mRNA\_translation).

$$\frac{d}{dt}IAAm = |v_3| + |v_6| - |v_4| - |v_6| \tag{34}$$

# 7.3 Species IAAp

# Name IAAp

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

This species takes part in six reactions (as a reactant in IAA\_degradation, ARFIAA\_formation, auxTIR1IAA\_formation and as a product in mRNA\_translation, ARFIAA\_dissociation, auxTIR1IAA\_dissociation).

$$\frac{\mathrm{d}}{\mathrm{d}t}IAAp = |v_6| + |v_{10}| + |v_{14}| - |v_5| - |v_9| - |v_{13}| \tag{35}$$

#### 7.4 Species ARF

#### Name ARF

#### Initial concentration $10 \text{ mol} \cdot l^{-1}$

This species takes part in five reactions (as a reactant in ARF2\_formation, ARFIAA\_formation and as a product in ARF2\_dissociation, ARFIAA\_dissociation and as a modifier in mRNA\_production).

$$\frac{d}{dt}ARF = 2 v_8 + v_{10} - 2 v_7 - v_9 \tag{36}$$

# 7.5 Species null

#### Name null

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

This species takes part in six reactions (as a reactant in auxin\_production, mRNA\_production and as a product in auxin\_degradation, mRNA\_degradation, IAA\_degradation, IAAstar\_degradation), which do not influence its rate of change because this constant species is on the boundary of the reaction system:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{null} = 0\tag{37}$$

# 7.6 Species ARFIAA

#### Name ARFIAA

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

This species takes part in three reactions (as a reactant in ARFIAA\_dissociation and as a product in ARFIAA\_formation and as a modifier in mRNA\_production).

$$\frac{\mathrm{d}}{\mathrm{d}t} ARFIAA = |v_9| - |v_{10}| \tag{38}$$

# 7.7 Species ARF2

Name ARF2

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

This species takes part in three reactions (as a reactant in ARF2\_dissociation and as a product in ARF2\_formation and as a modifier in mRNA\_production).

$$\frac{\mathrm{d}}{\mathrm{d}t} ARF2 = |v_7| - |v_8| \tag{39}$$

# 7.8 Species auxTIR1

Name auxTIR1

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

This species takes part in five reactions (as a reactant in auxTIR1\_dissociation, auxTIR1IAA\_formation and as a product in auxTIR1\_formation, auxTIR1IAA\_dissociation, IAA\_ubiquitination).

$$\frac{d}{dt}auxTIR1 = |v_{11}| + |v_{14}| + |v_{15}| - |v_{12}| - |v_{13}|$$
(40)

# 7.9 Species auxTIR1IAA

Name auxTIR1IAA

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

This species takes part in three reactions (as a reactant in auxTIR1IAA\_dissociation, IAA-ubiquitination and as a product in auxTIR1IAA\_formation).

$$\frac{d}{dt}auxTIR1IAA = |v_{13}| - |v_{14}| - |v_{15}|$$
 (41)

# 7.10 Species TIR1

Name TIR1

Initial concentration  $18.51 \text{ mol} \cdot l^{-1}$ 

This species takes part in two reactions (as a reactant in auxTIR1\_formation and as a product in auxTIR1\_dissociation).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{TIR1} = v_{12} - v_{11} \tag{42}$$

# 7.11 Species IAAstar

#### Name IAAstar

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

This species takes part in two reactions (as a reactant in IAAstar\_degradation and as a product in IAA\_ubiquitination).

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{IAAstar} = |v_{15}| - |v_{16}| \tag{43}$$

 $\mathfrak{BML2}^{lAT}$ EX was developed by Andreas Dräger<sup>a</sup>, Hannes Planatscher<sup>a</sup>, Dieudonné M Wouamba<sup>a</sup>, Adrian Schröder<sup>a</sup>, Michael Hucka<sup>b</sup>, Lukas Endler<sup>c</sup>, Martin Golebiewski<sup>d</sup> and Andreas Zell<sup>a</sup>. Please see http://www.ra.cs.uni-tuebingen.de/software/SBML2LaTeX for more information.

<sup>&</sup>lt;sup>a</sup>Center for Bioinformatics Tübingen (ZBIT), Germany

<sup>&</sup>lt;sup>b</sup>California Institute of Technology, Beckman Institute BNMC, Pasadena, United States

<sup>&</sup>lt;sup>c</sup>European Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom

<sup>&</sup>lt;sup>d</sup>EML Research gGmbH, Heidelberg, Germany