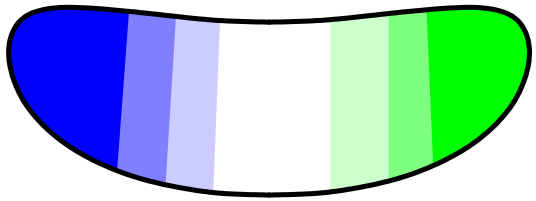
Robustness in *Drosophila* Segment Polarity

Nicholas Ingolia

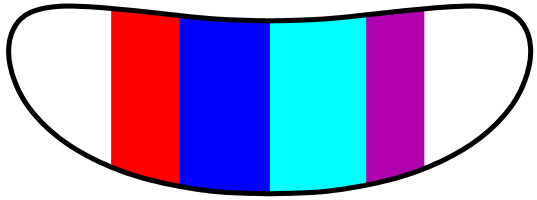
Harvard University

Hierarchy of Segmentation Genes

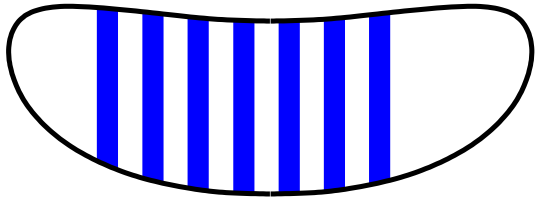
Maternal Genes



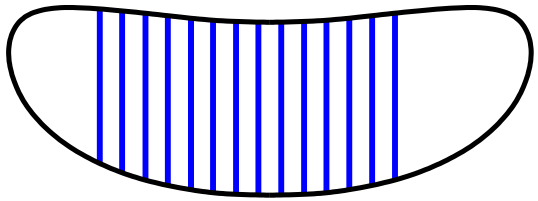
Gap Genes



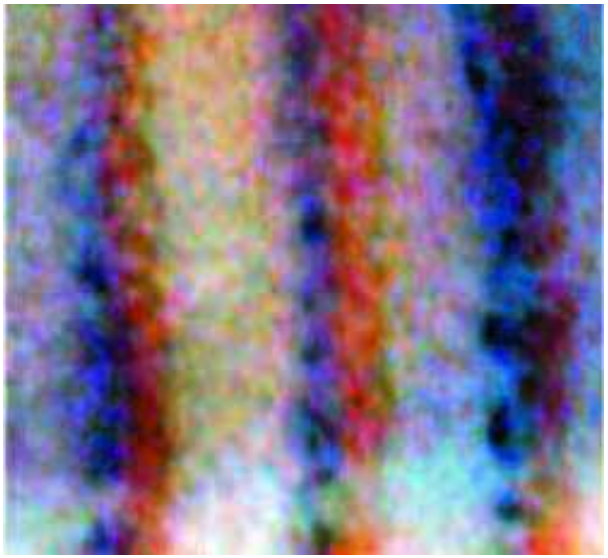
Pair–Rule Genes



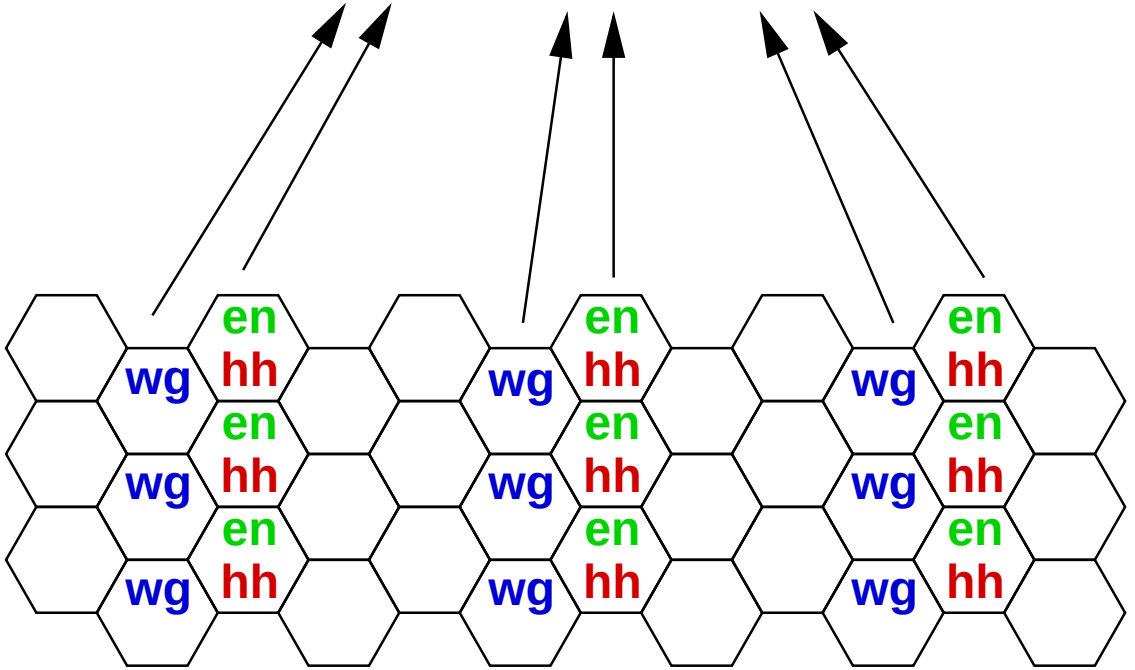
Segment Polarity Genes



Segment Polarity Pattern



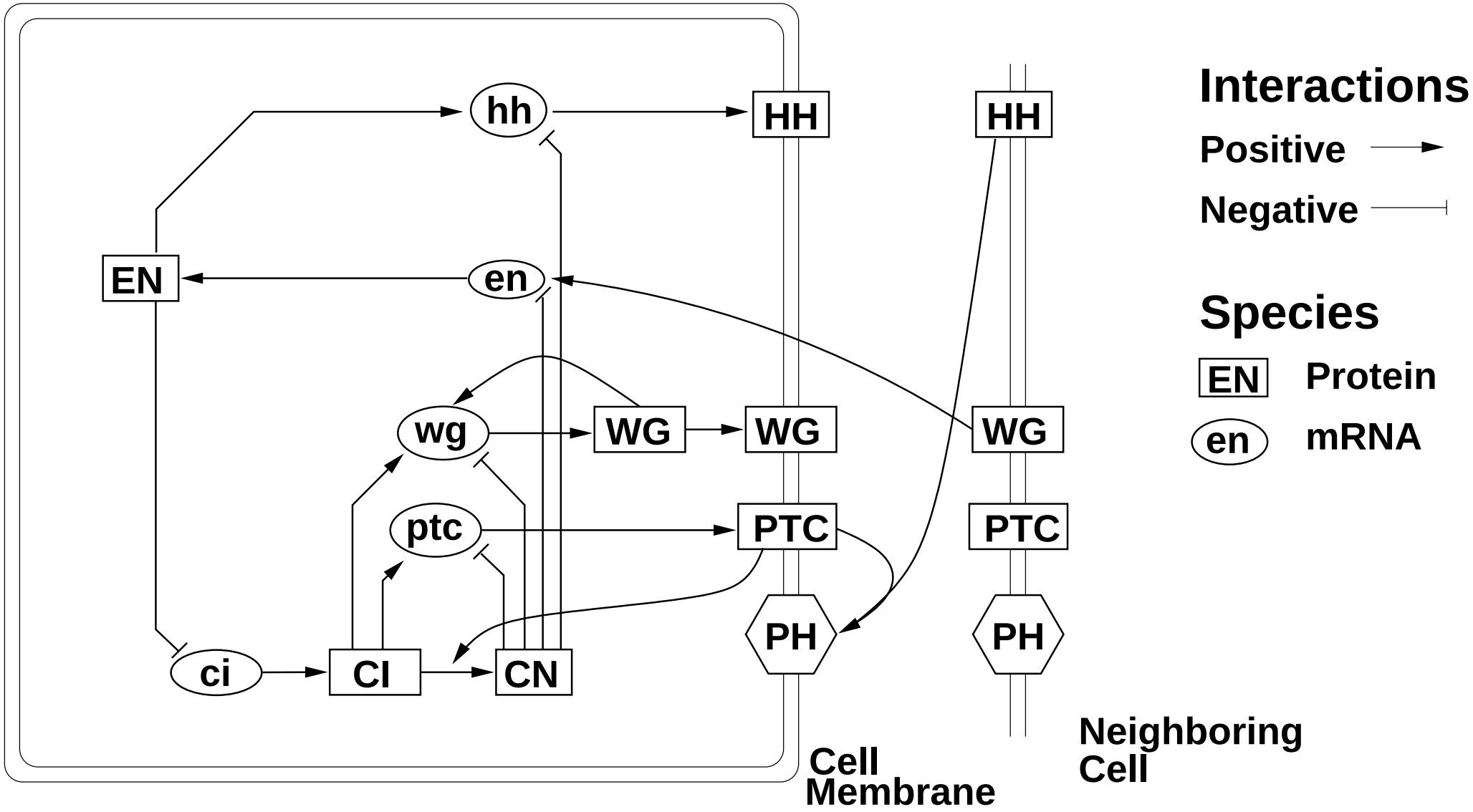
Gallet, Angelats,
Kerridge, & Therond 2000



Anterior

Posterior

Segment Polarity Gene Network



Segment Polarity Model

32 dynamic variables per cell

16 cells per lattice

512 dynamic variables

Segment Polarity Model

32 dynamic variables per cell

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16 cells per lattice

50 parameters in 12 distinct ODEs

Segment Polarity Model

32 dynamic variables per cell

512 dynamic variables

16 cells per lattice

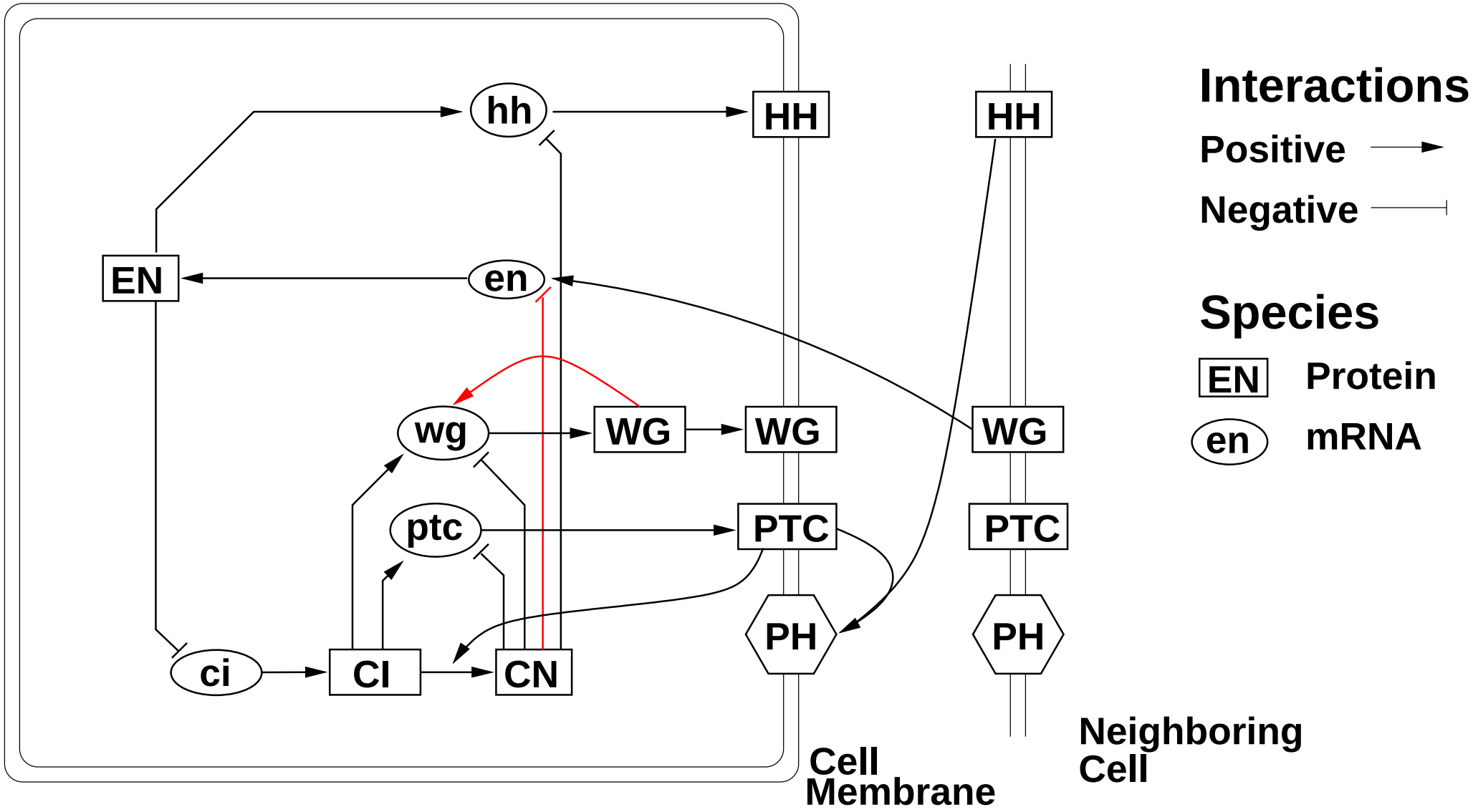
50 parameters in 12 distinct ODEs

Random parameter sets: 0.5% form the segment polarity pattern

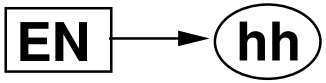
"The most striking systems–level property...is robustness"

"We originally expected the core topology to be frail and easily perturbed....the simplest model...emerged complete with unexpected robustness"

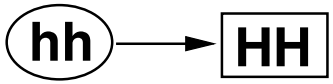
Segment Polarity Gene Network



Segment Polarity Model Equations



$$\frac{dhh}{dt} = \frac{1}{\tau_{hh}}\left(-hh + \frac{EN^{\nu}}{K^{\nu} + EN^{\nu}}\right)$$



$$\frac{dHH}{dt} = \frac{1}{\tau_{HH}}\left(-HH + hh\right)$$

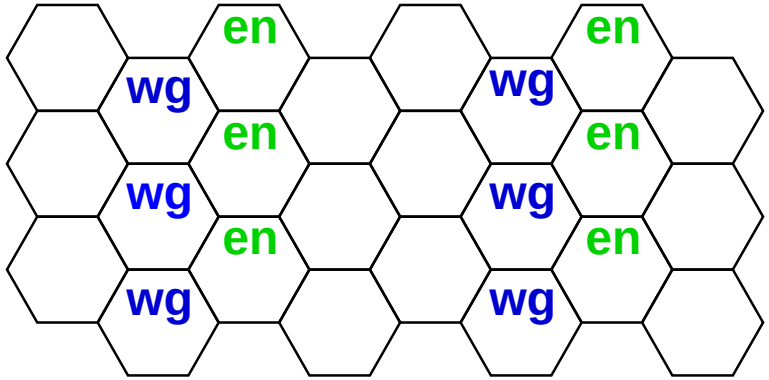
τ_{hh} Time constant of hh degradation

K "Affinity" of EN: level needed for half–maximal response

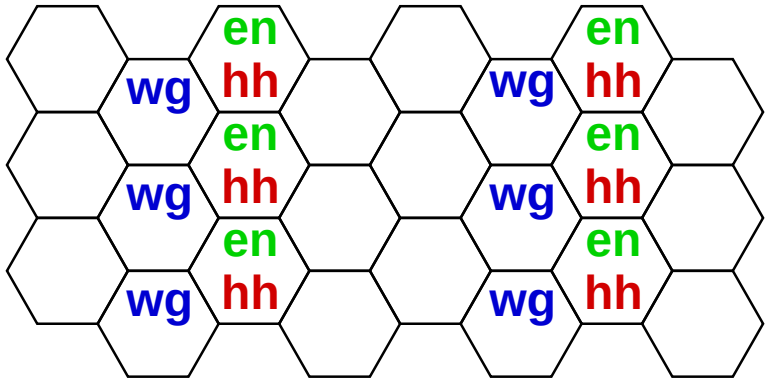
ν Cooperativity

Segment Polarity Pattern

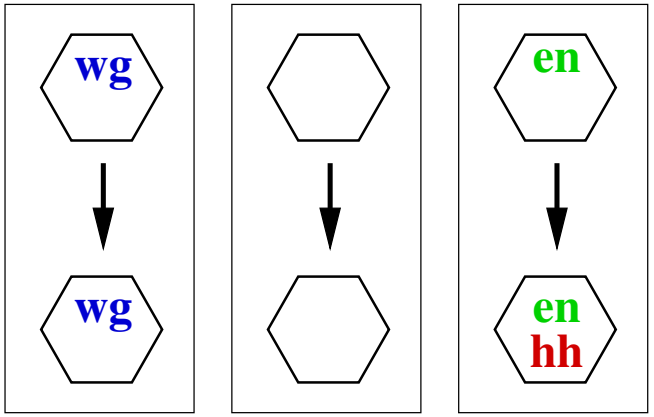
Prepattern



Final Pattern



Single–Cell Behaviors



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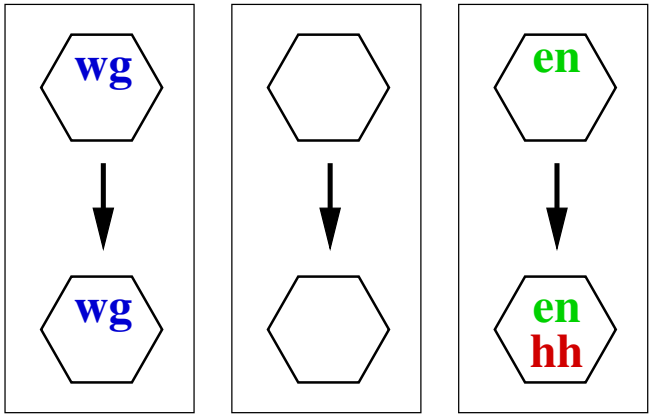

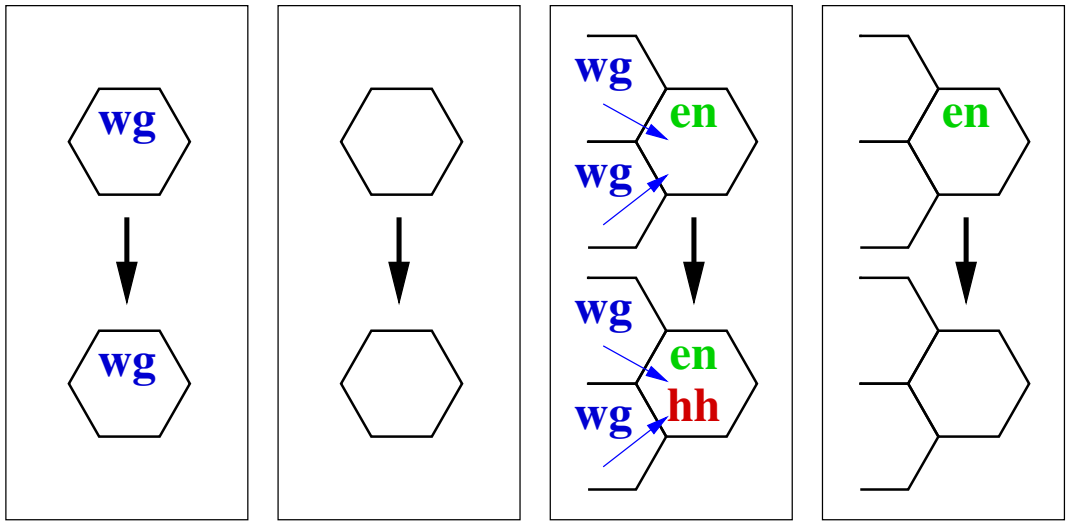

Bistability Predicts Pattern Formation

		Pattern Formation +	Pattern Formation –	Total	Predictive Value
Single–Cell Behavior	**+**	0.52	0.57	1.1	0.47
	–	0.01*	99.	99.	1.00
		0.53	99.		

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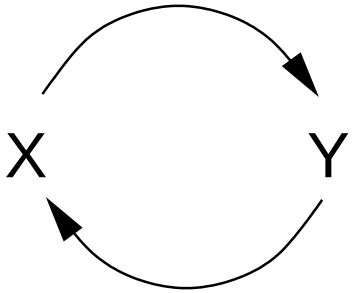
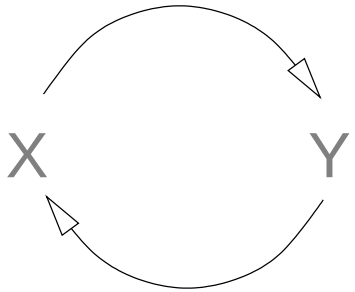
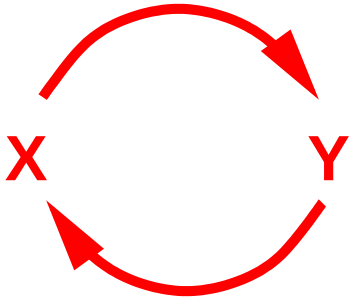
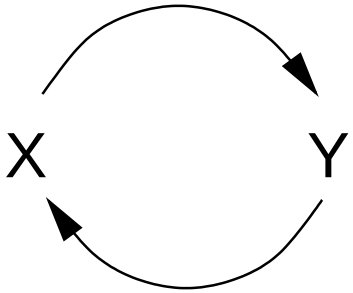
Positve Feedback and Bistability

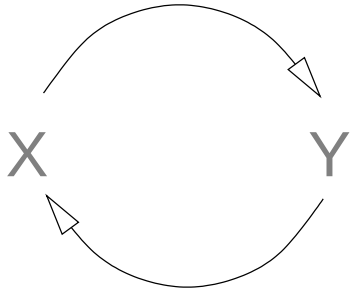


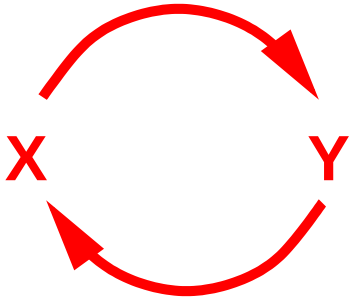


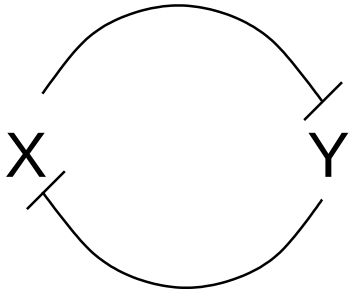


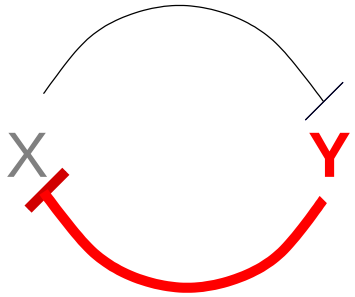
Positive Feedback and Bistability

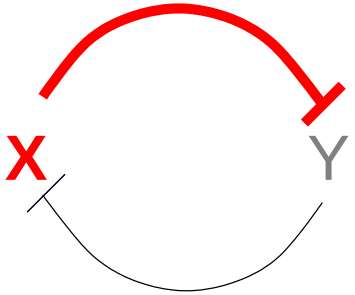




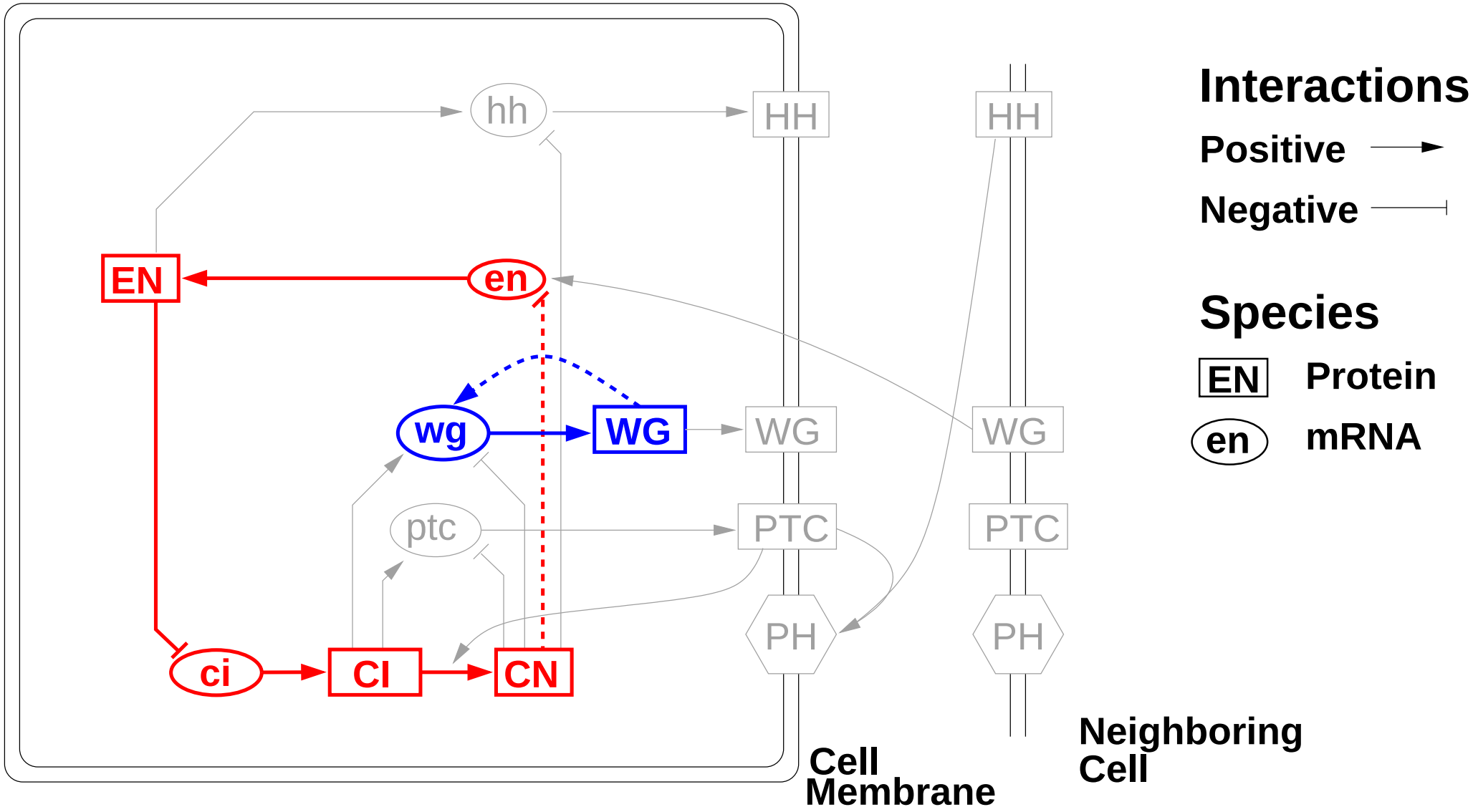




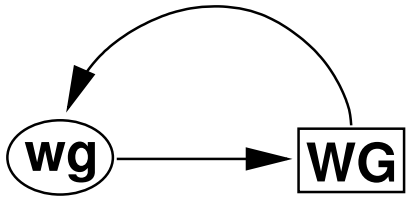




Segment Polarity Gene Network

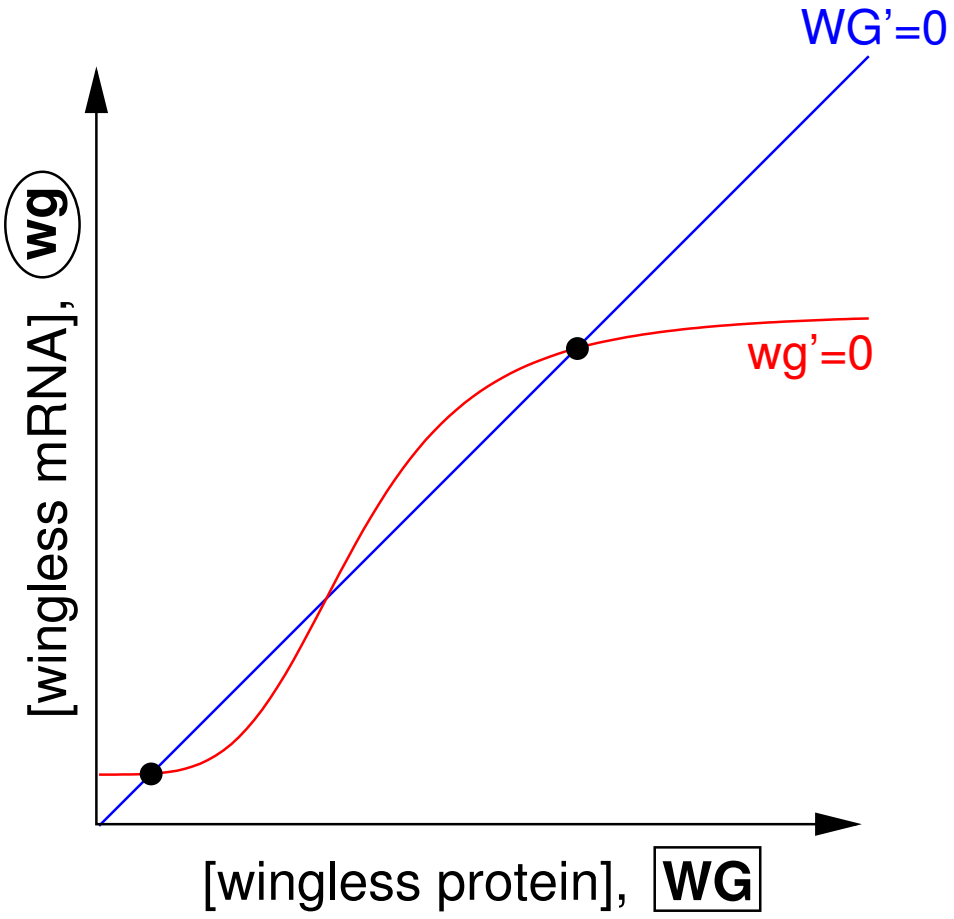


Bistability and Positive Feedback



$$\frac{dwg}{dt} = \frac{1}{\tau_{wg}}\left(-wg + \frac{\beta K^{\nu} + WG^{\nu}}{K^{\nu} + WG^{\nu}}\right)$$

$$\frac{dWG}{dt} = \frac{1}{\tau_{WG}}\left(-WG + wg\right)$$

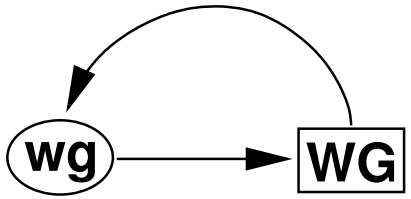


$K = .5$

$\beta = .1$

$\nu = 4$

Bistability and Positive Feedback



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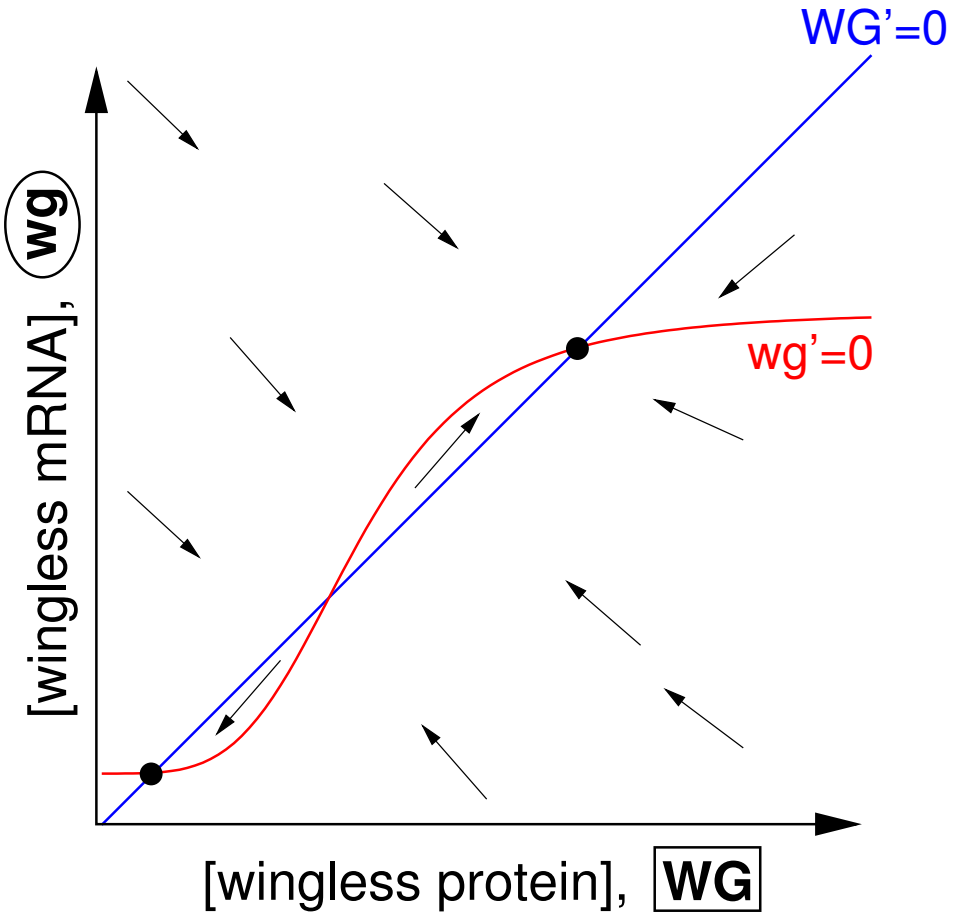

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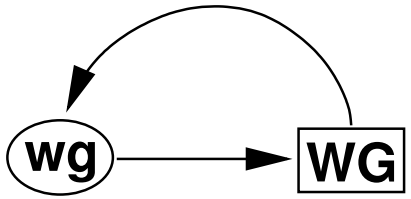
Bistability and Positive Feedback



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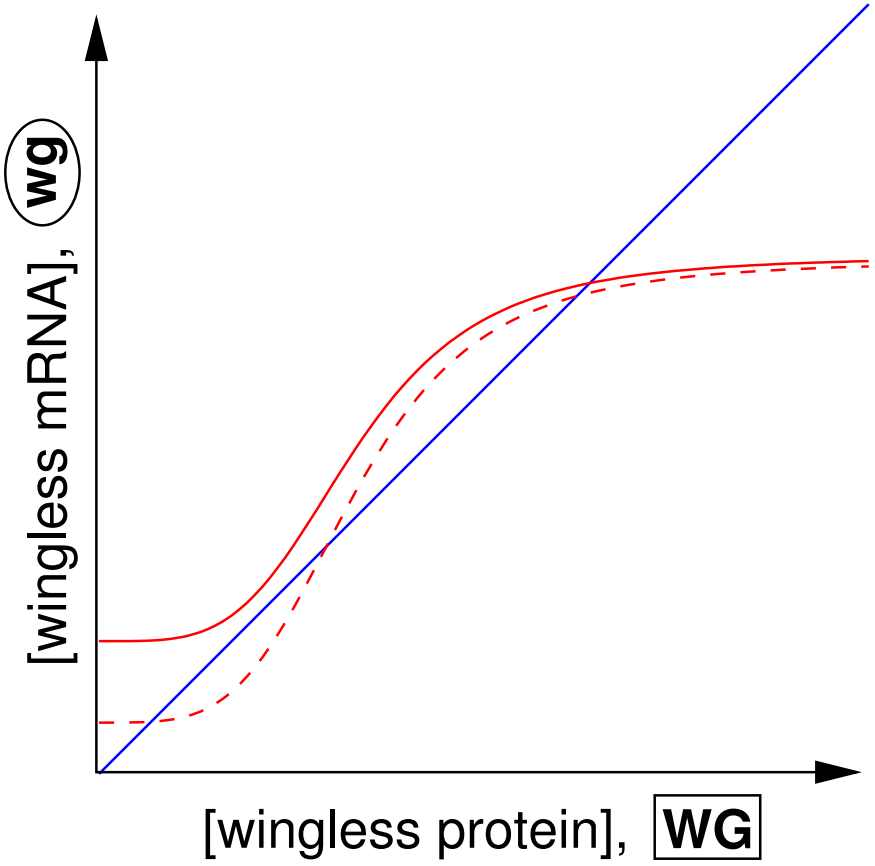

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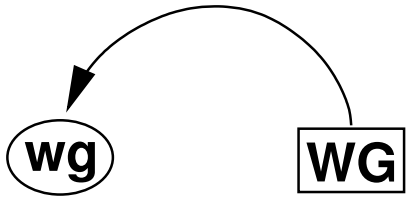

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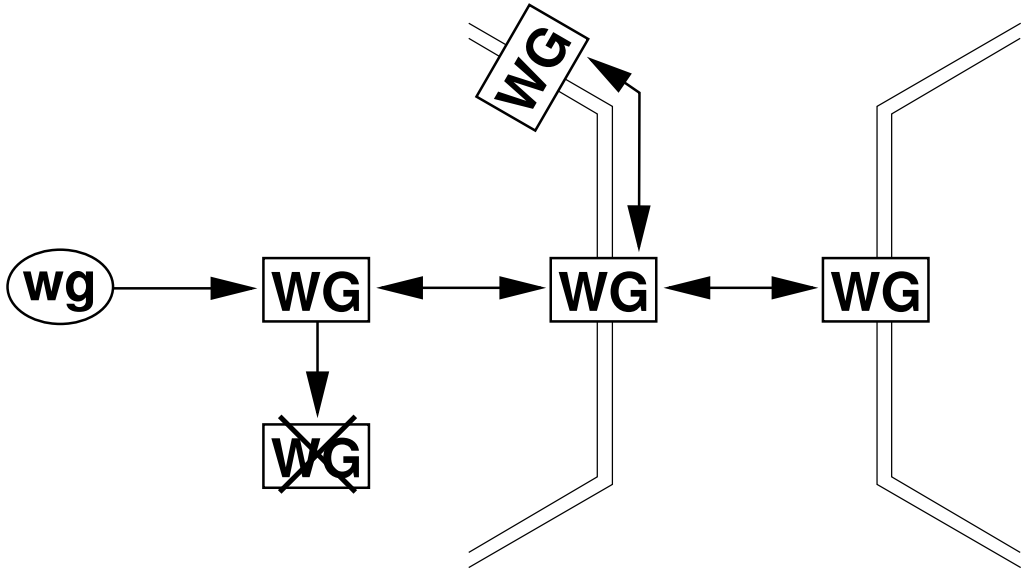
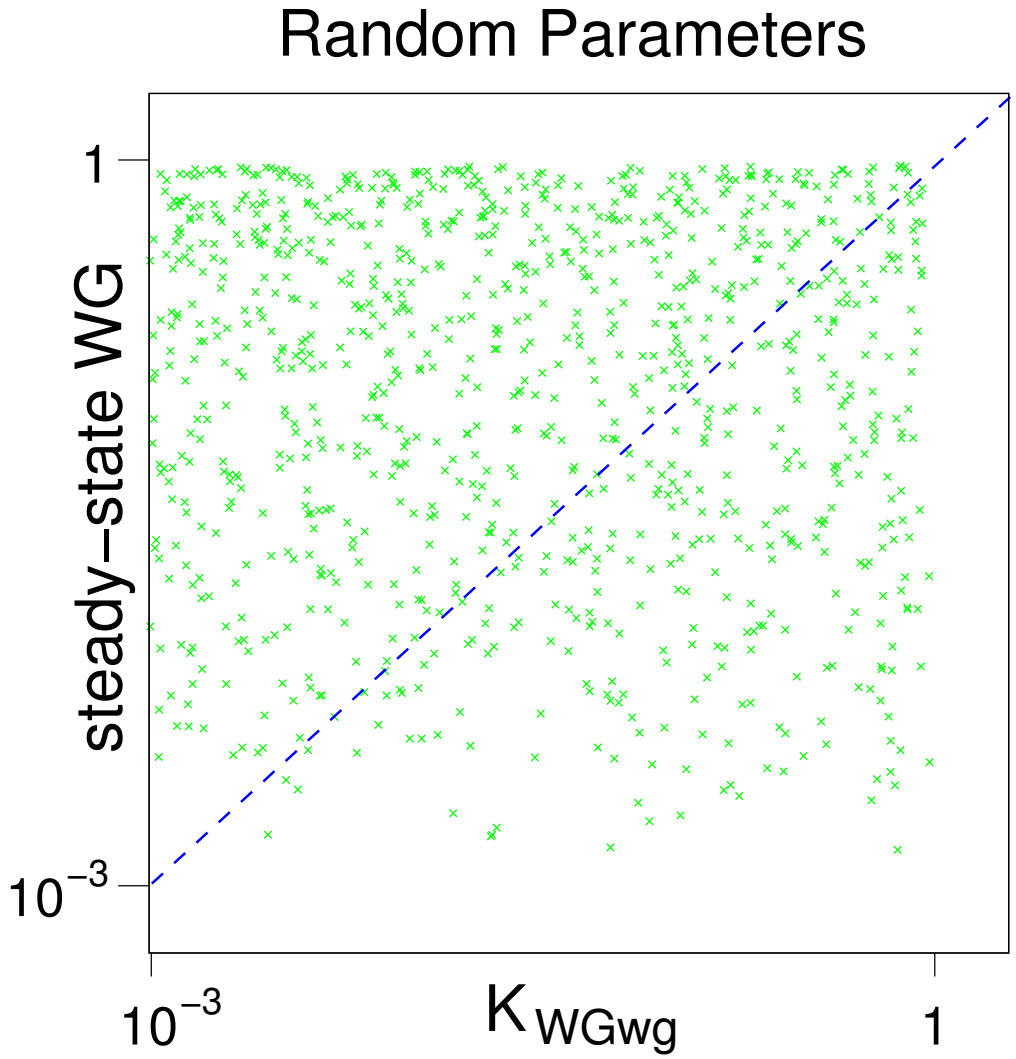


K_{WGwg} < steady–state [intracellular WG]

Bistability Predicts Pattern Formation



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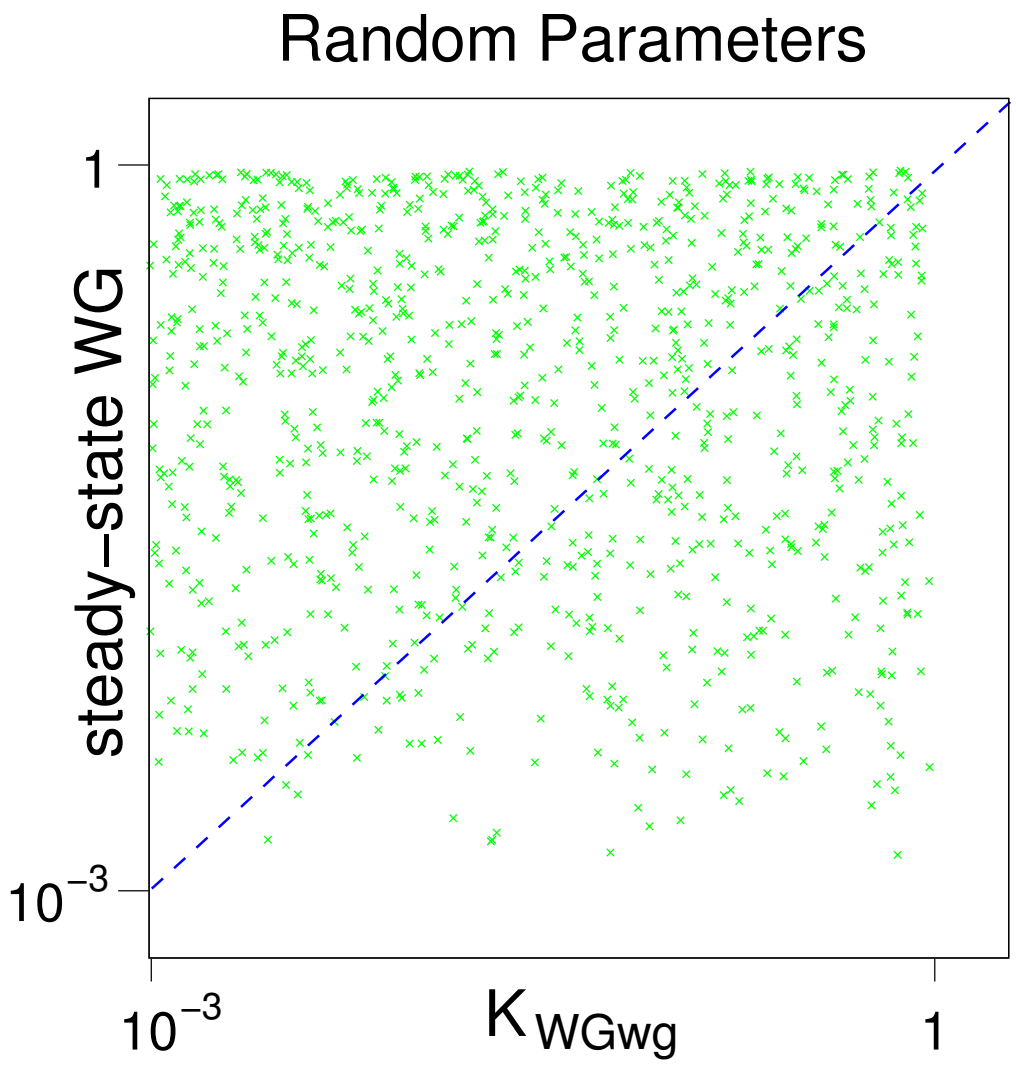

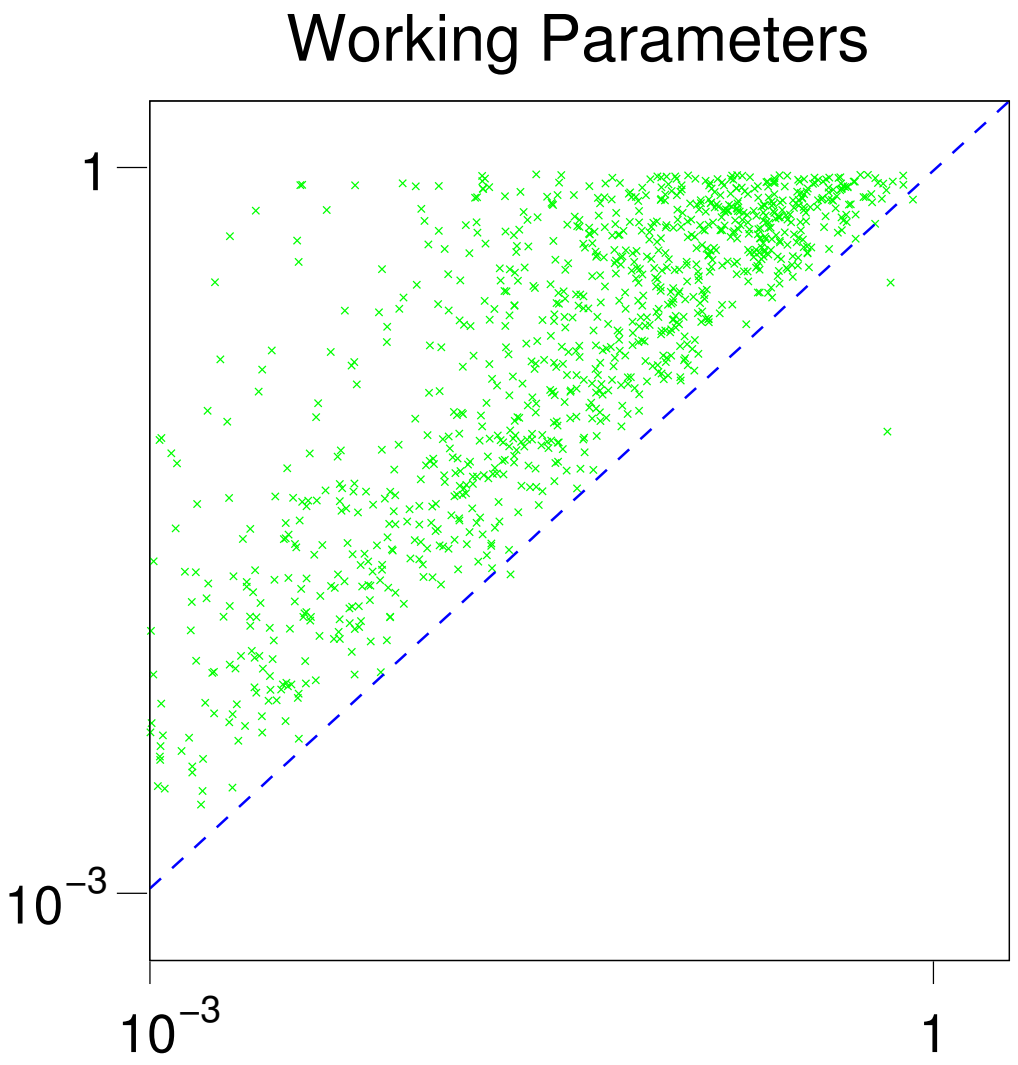

Bistability Predicts Pattern Formation

		Pattern Formation			Predictive Value
		+	–	Total	
Single–Cell Behavior	+	0.52	0.57	1.1	0.47
	–	0.01*	99.	99.	1.00
		0.53	99.		
Bistability	+	0.56	7.6	8.2	0.07
	–	0.05	92.	92.	1.00
		0.61	99.		

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	–	0.05	92.	92.	1.00
		0.61	99.		
modified prepattern	+	3.4	4.8	8.2	0.41
	–	0.22	92.	92.	1.00
		3.6	96.		

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		0.61	99.		
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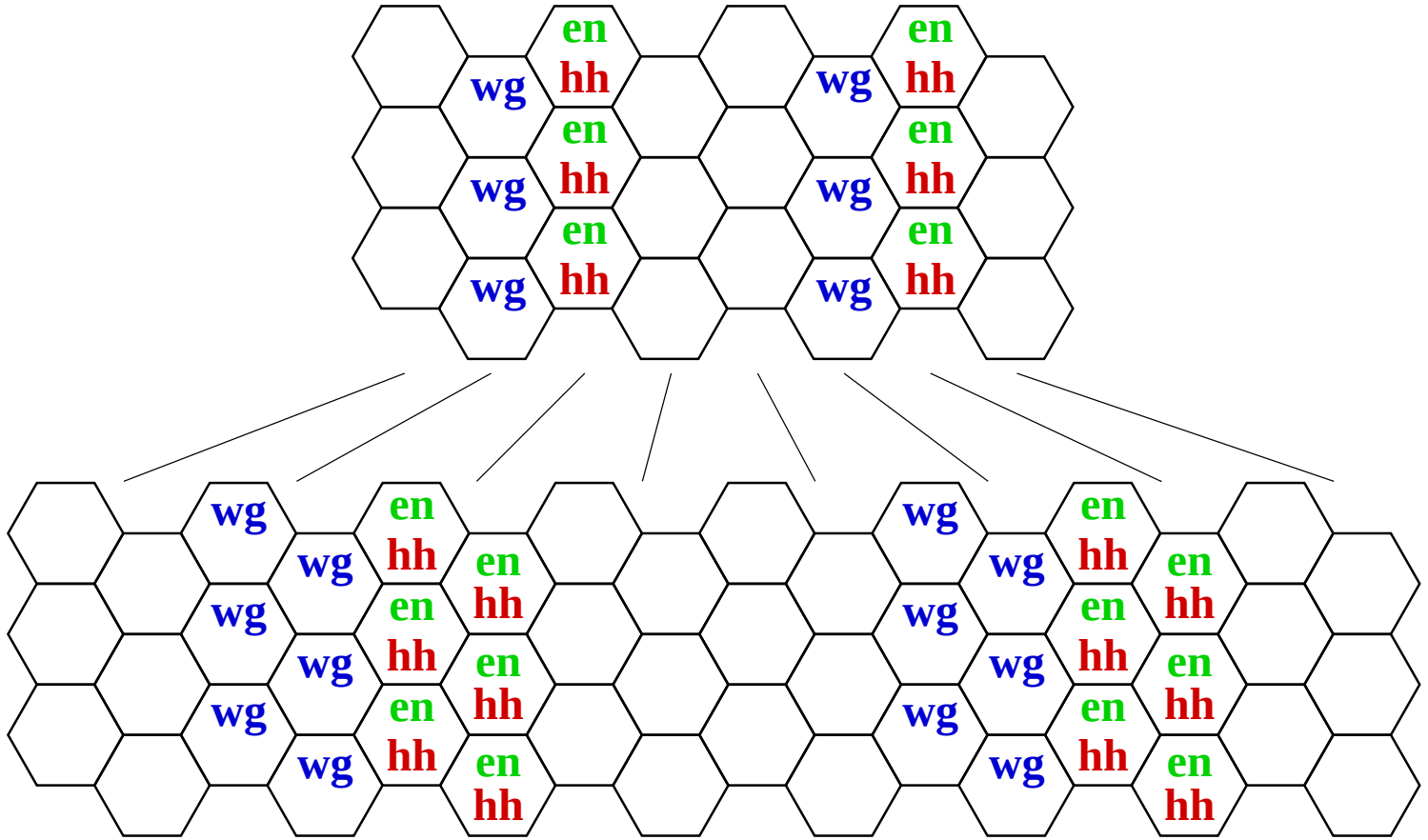
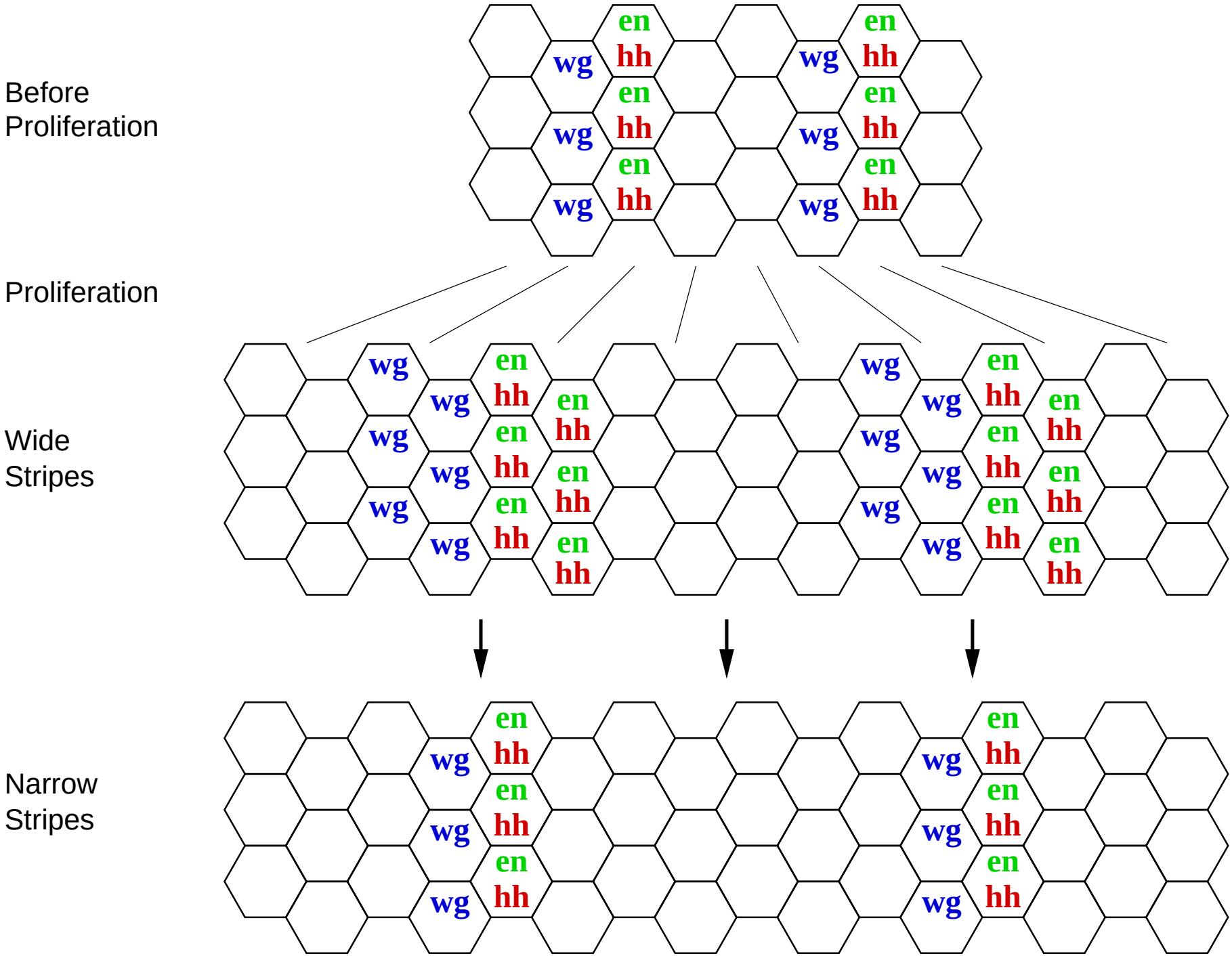
	–	0.22	92.	92.	1.00
		3.6	96.		

Before Proliferation

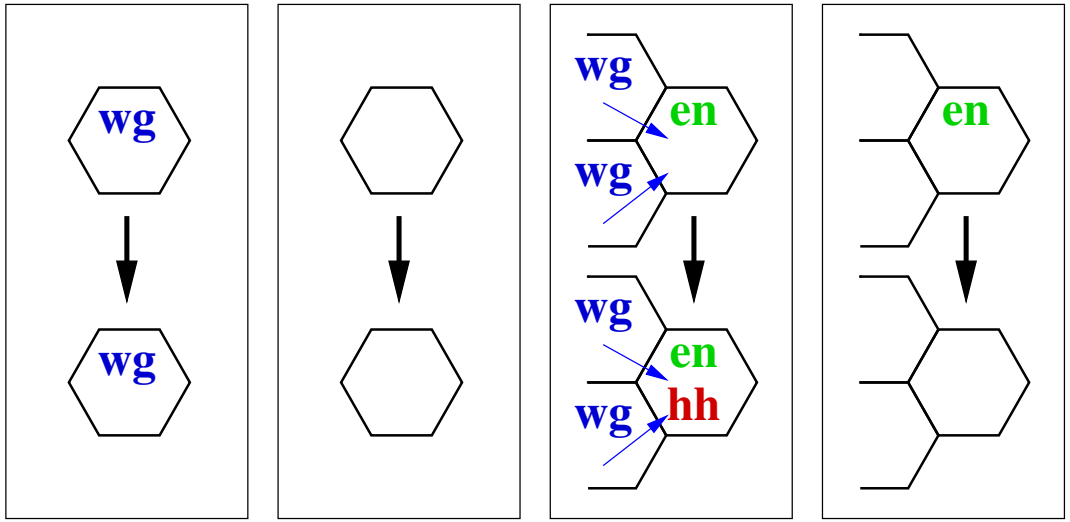
Proliferation

Wide Stripes




Before Proliferation
Proliferation
Wide Stripes
Narrow Stripes
wg
en
hh

Single–Cell Behaviors



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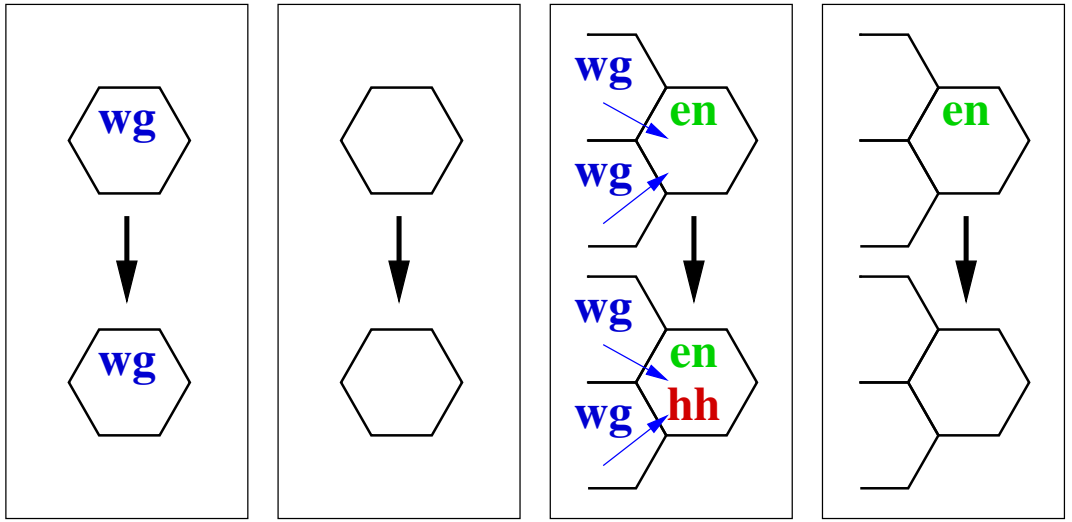
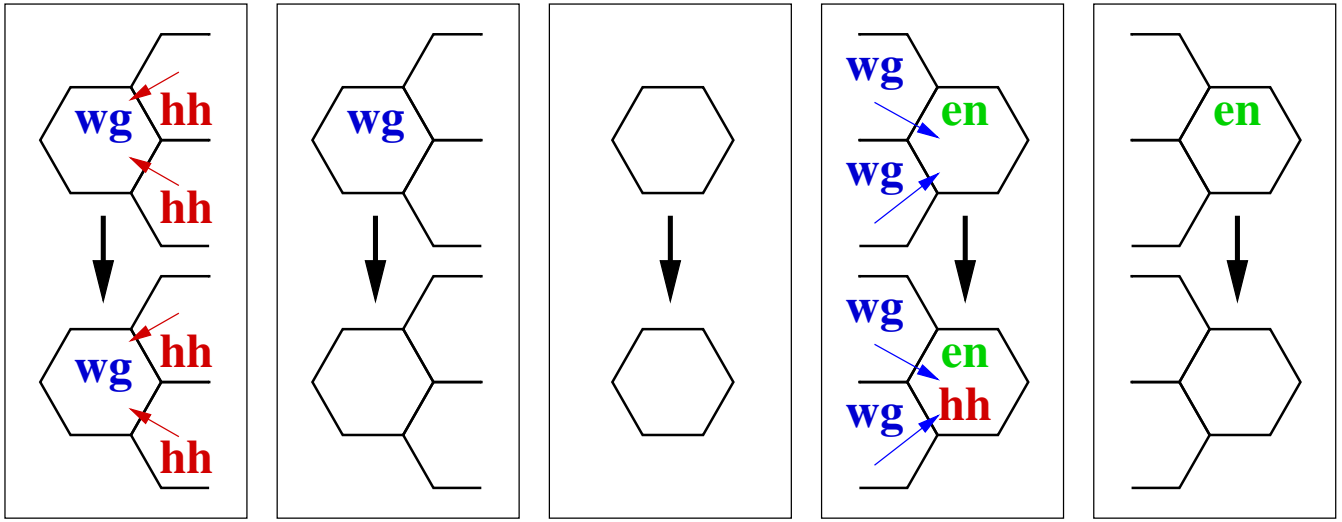
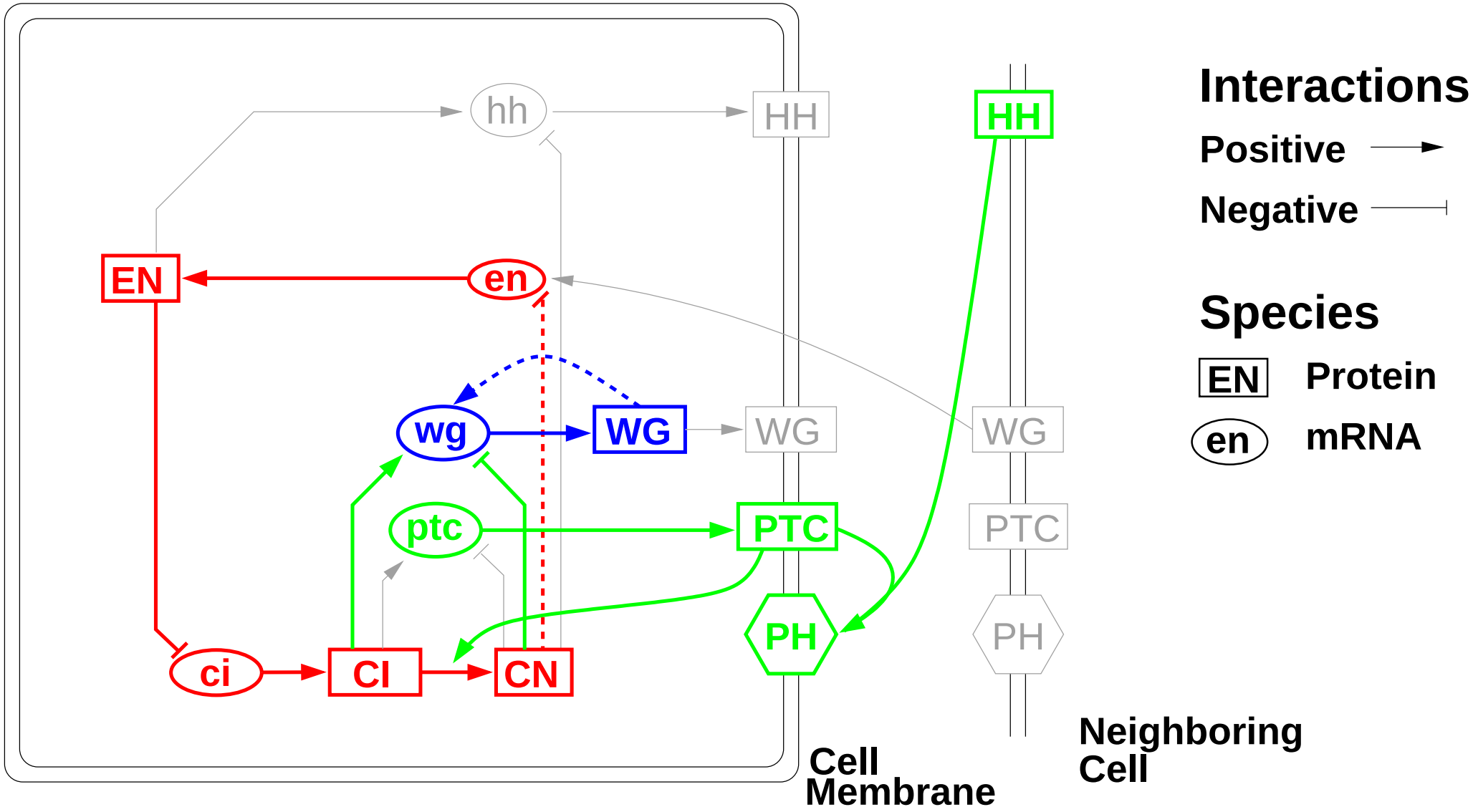




Segment Polarity Gene Network



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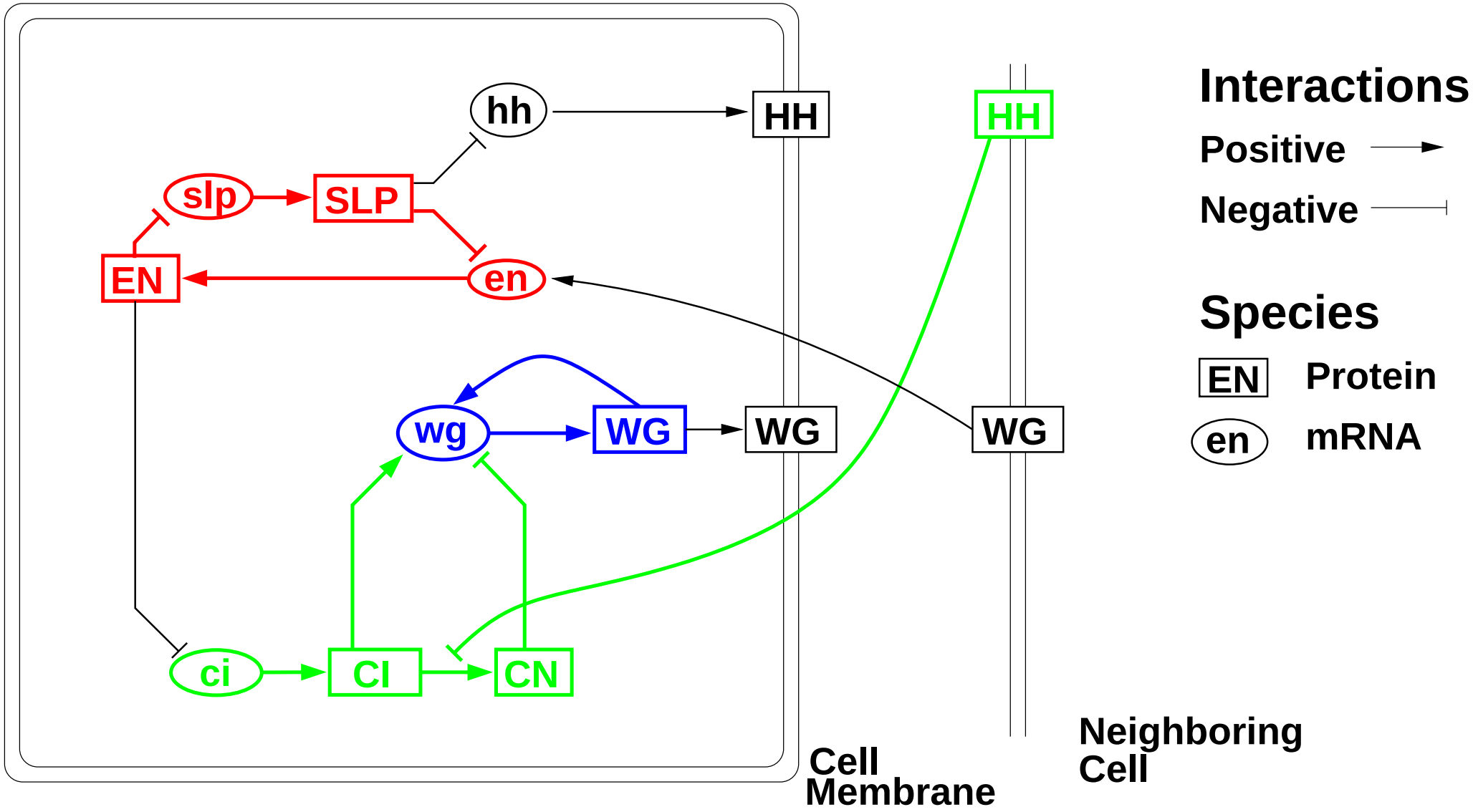
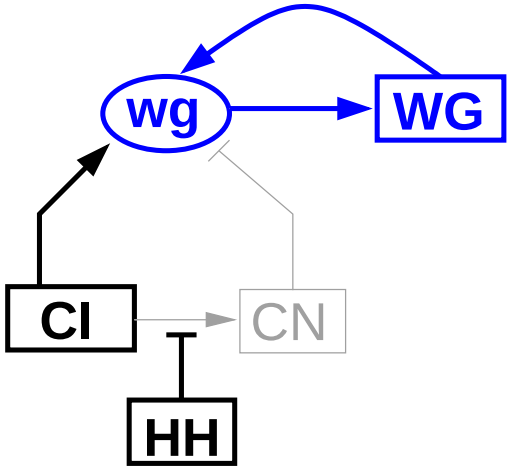


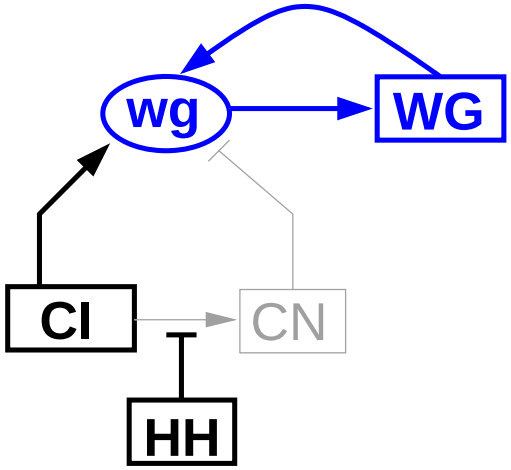
Bistability Predicts Proliferation Behavior

4–Cell Patterning	+	9.6	**Proliferation**	+	1.7
	–	90.		–	8.0

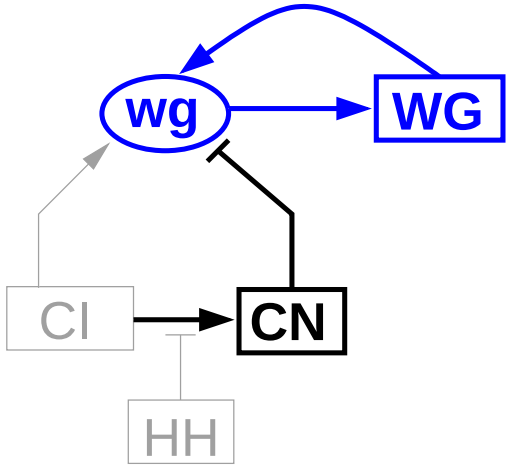
Proliferation and Positive Feedback



Proliferation and Positive Feedback

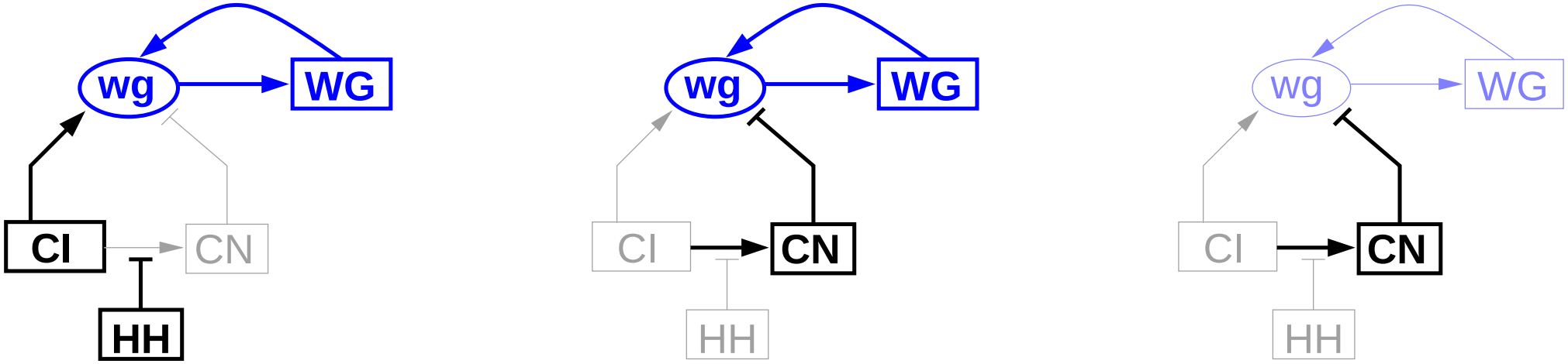


Stable



Unstable

Proliferation and Positive Feedback

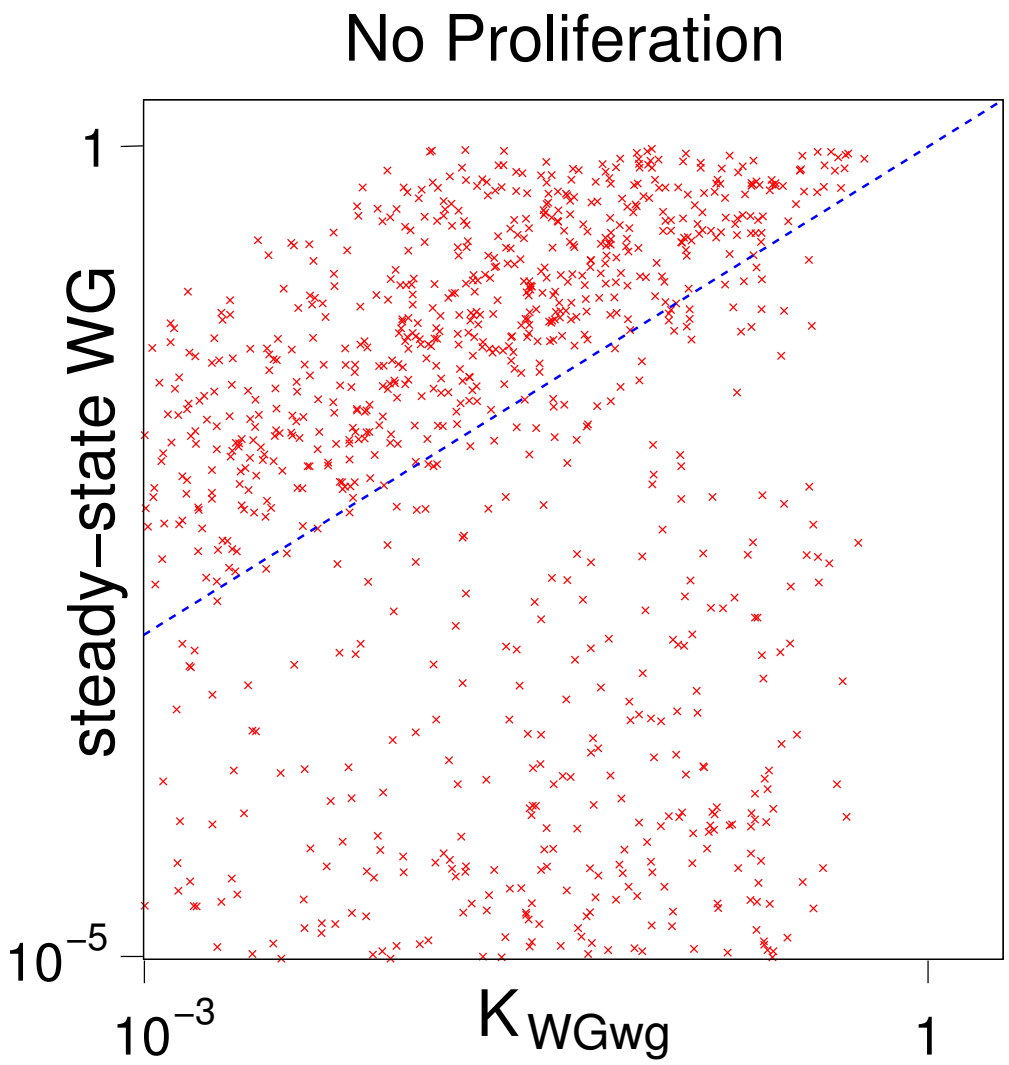


Stable

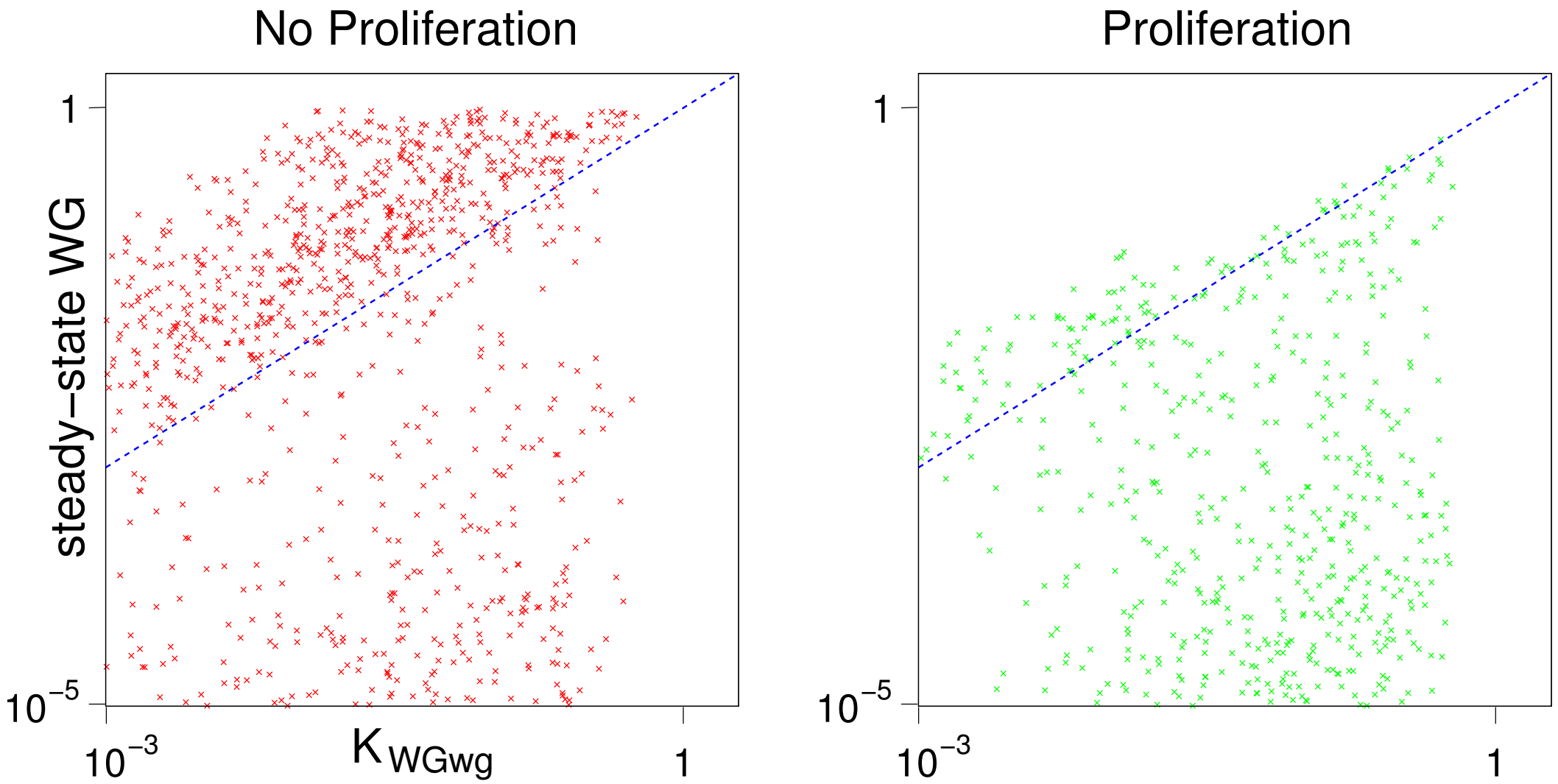
Unstable

Stable

Bistability Predicts Proliferation



Bistability Predicts Proliferation



Bistability Predicts Proliferation Behavior

4–Cell Patterning	**+**	9.6	**Proliferation**	**+**	1.7
	–	90.		**–**	8.0

		Proliferation			**Predictive Value**
		+	**–**	**Total**	
Bistability	**+**	14.	19.	33.	0.42
	–	3.3	64.	67.	0.95
		17.	83.		

Bistability Predicts Proliferation Behavior

4–Cell Patterning			Proliferation		
	+	9.6		+	1.7
	–	90.		–	8.0

Bistability	Proliferation +	Proliferation –	Total	Predictive Value
+	14.	19.	33.	0.42
–	3.3	64.	67.	0.95
	17.	83.		

Bistability Predicts Proliferation Behavior

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Bistability	Proliferation +	Proliferation –	Total	Predictive Value
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Conclusions

Robustness:

Pattern is a stable steady state

Conclusions

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Individual cell stable steady states plus interactions

Conclusions

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Pattern is a stable steady state

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Bistability from positive feedback

Acknowledgements

Andrew Murray

Daniel Fisher

NIH

HHMI