Robustness of Stochastic Biochemical Systems

Sven Dražan

19. 3. 2013

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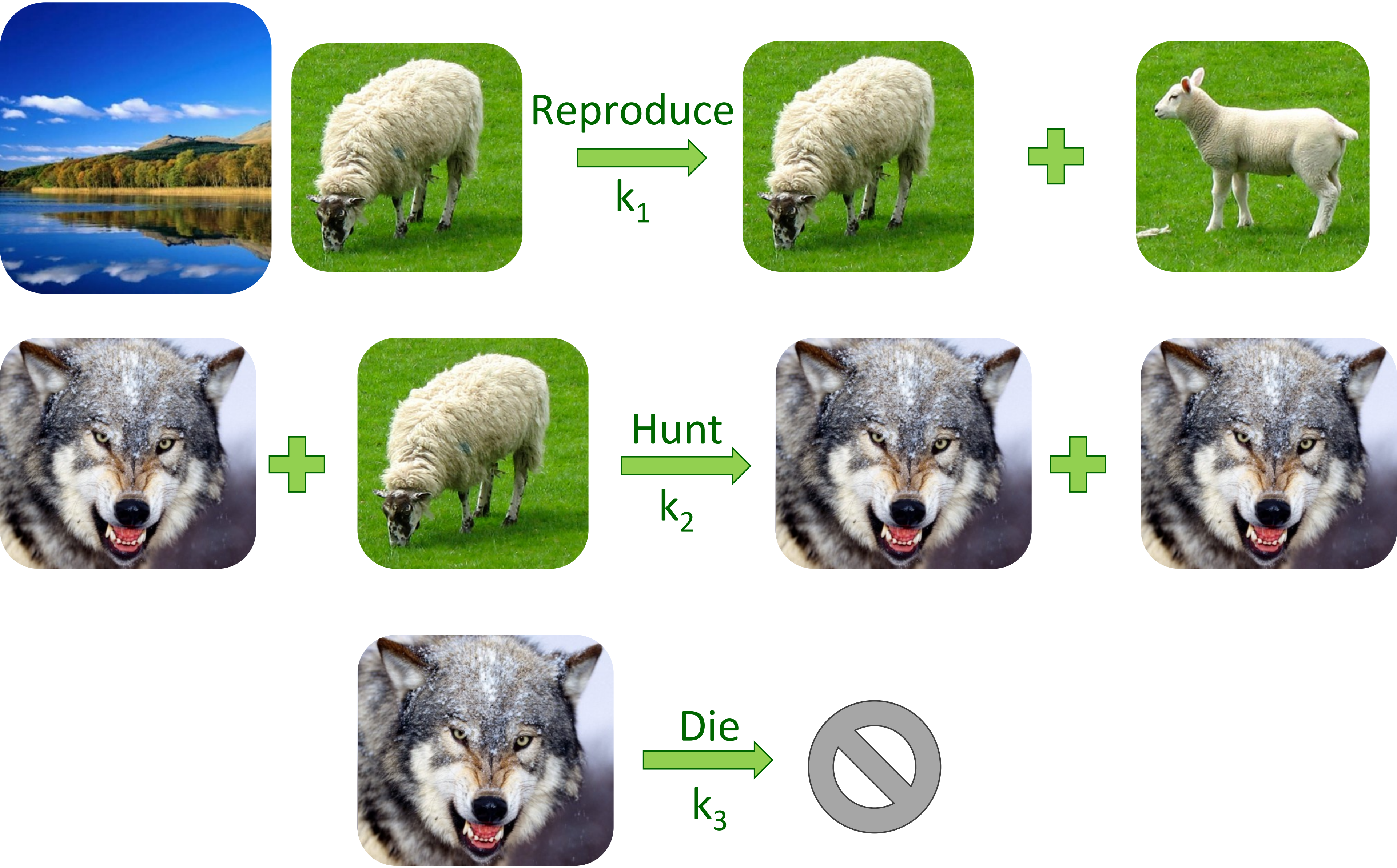
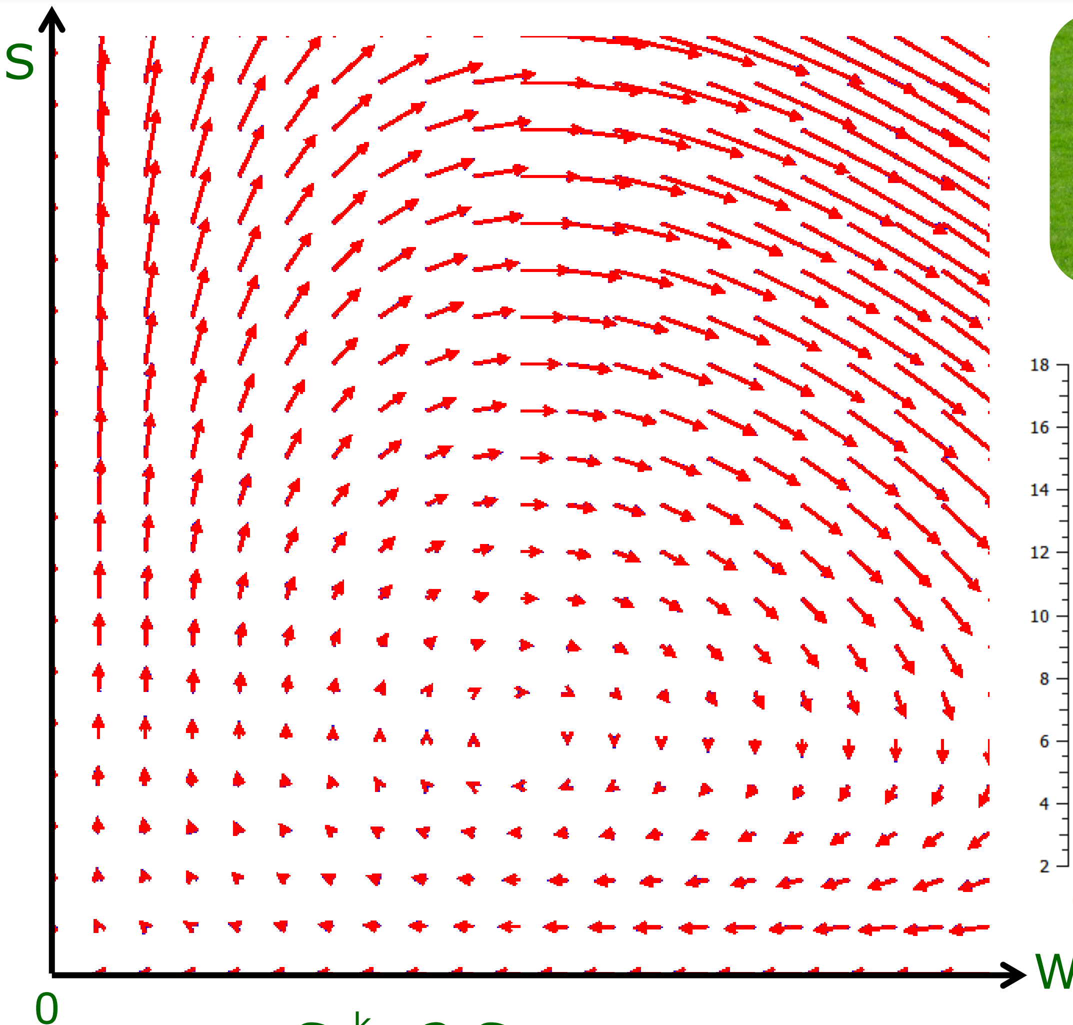
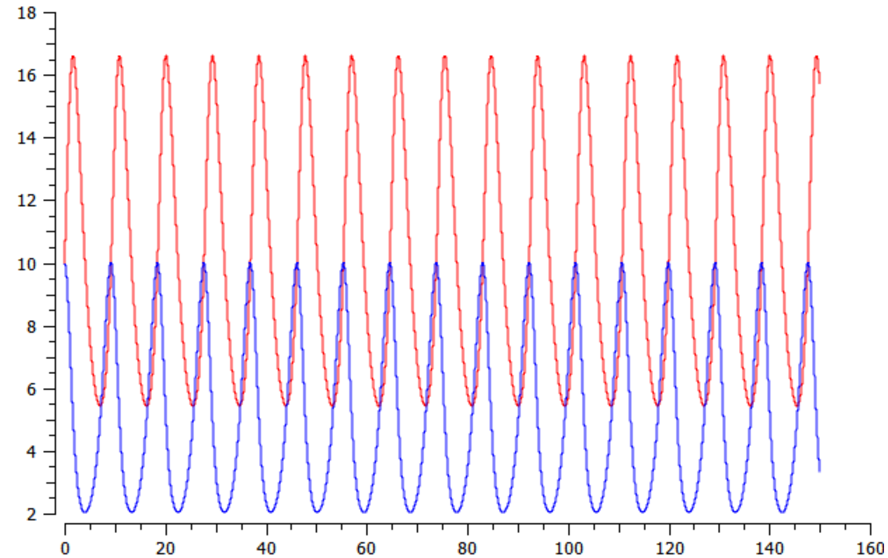
- Systems + Properties + Perturbations = Robustness
- Aims
- Preliminary results

Biochemical system



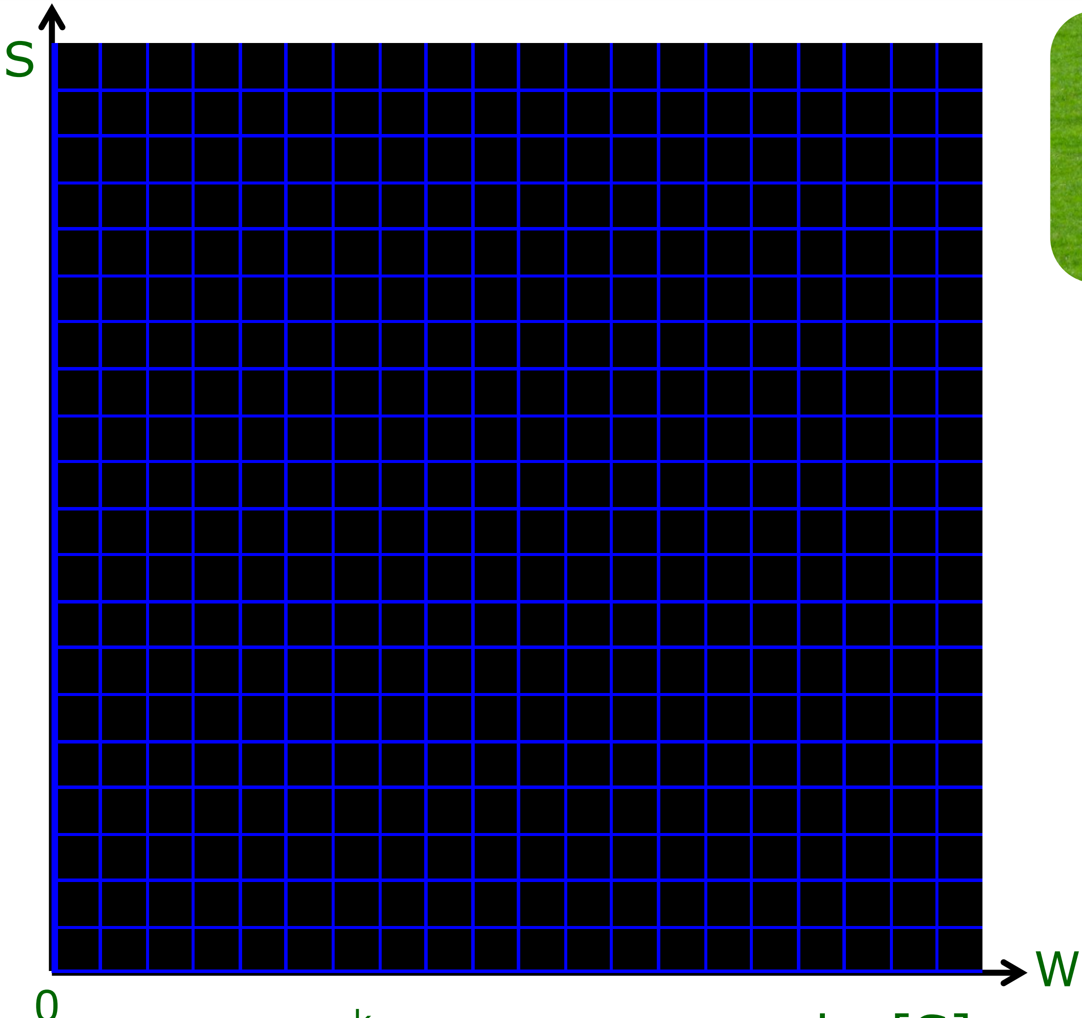
Biochemical system – Continuous / ODEs





$$S \xrightarrow{k_1} 2\,S$$
$$W + S \xrightarrow{k_2} 2\,W$$
$$W \xrightarrow{k_3}$$

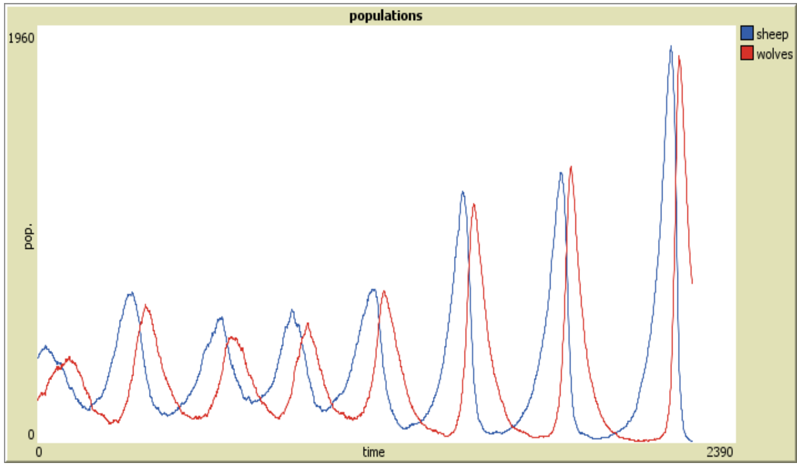
$$dS/dt = k_1.[S] - k_2.[W].[S]$$
$$dW/dt = k_2.[W].[S] - k_3.[W]$$

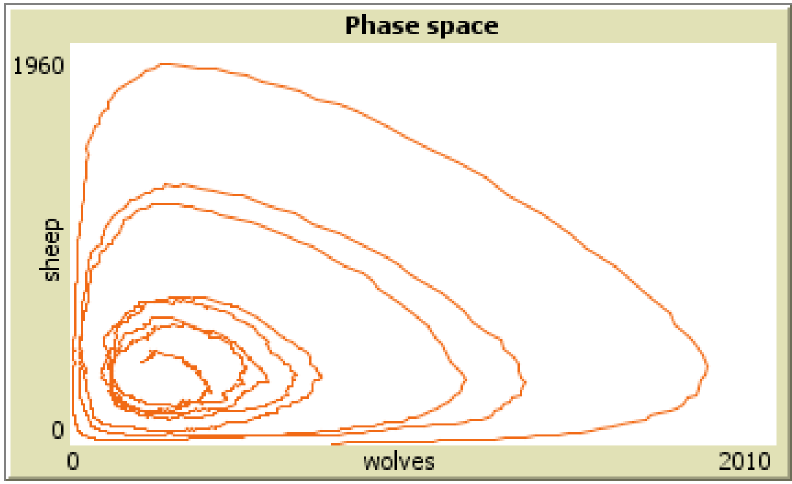


$S \xrightarrow{k_1} 2\,S$ $\quad a_1 = k_1.[S]$

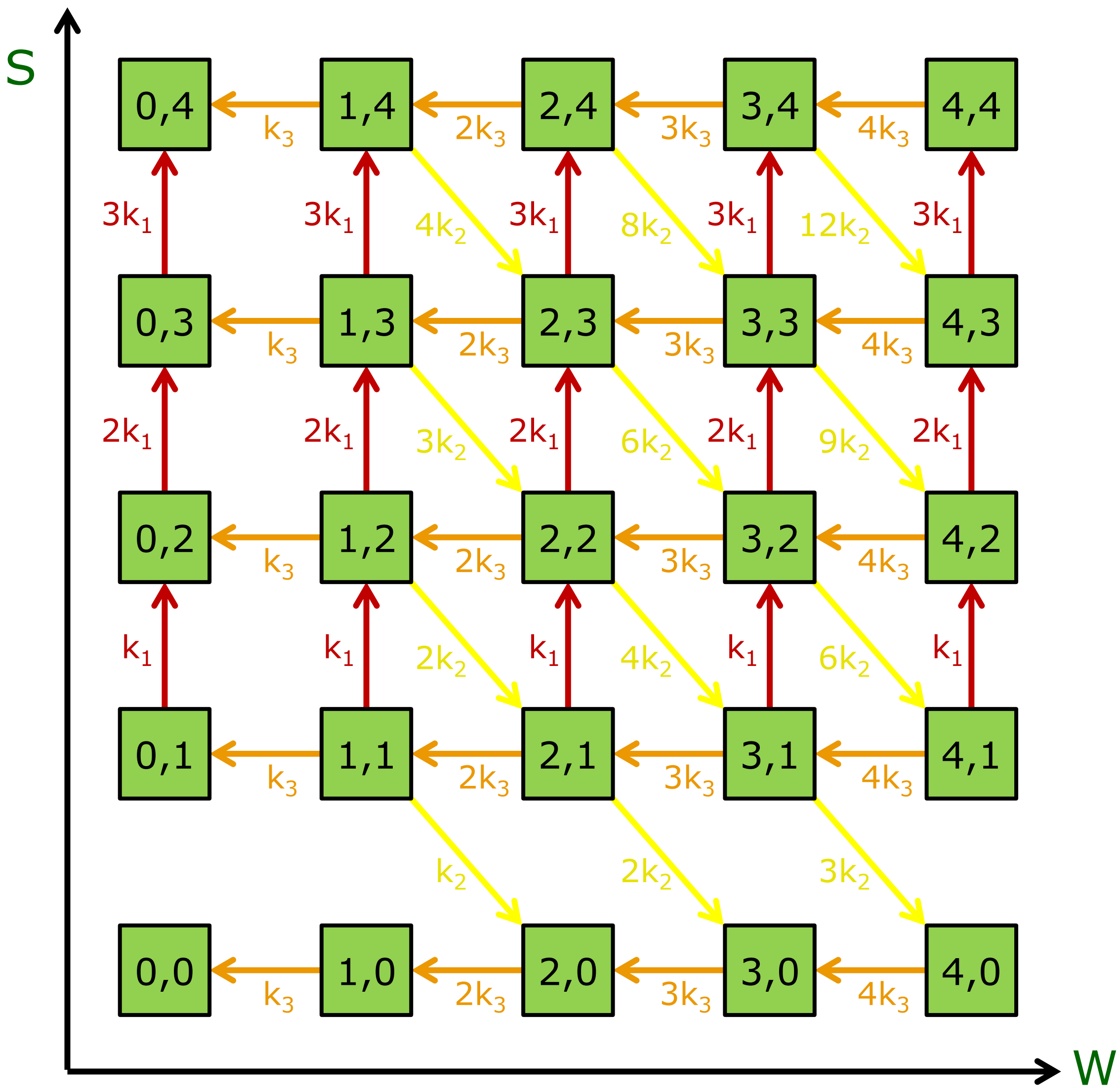
$W + S \xrightarrow{k_2} 2\,W$ $\quad a_2 = k_2.[W].[S]$

$W \xrightarrow{k_3}$ $\quad a_3 = k_3.[W]$





Biochemical system – Stochastic / CTMC



$$S \xrightarrow{k_1} 2\,S$$

$$W + S \xrightarrow{k_2} 2\,W$$

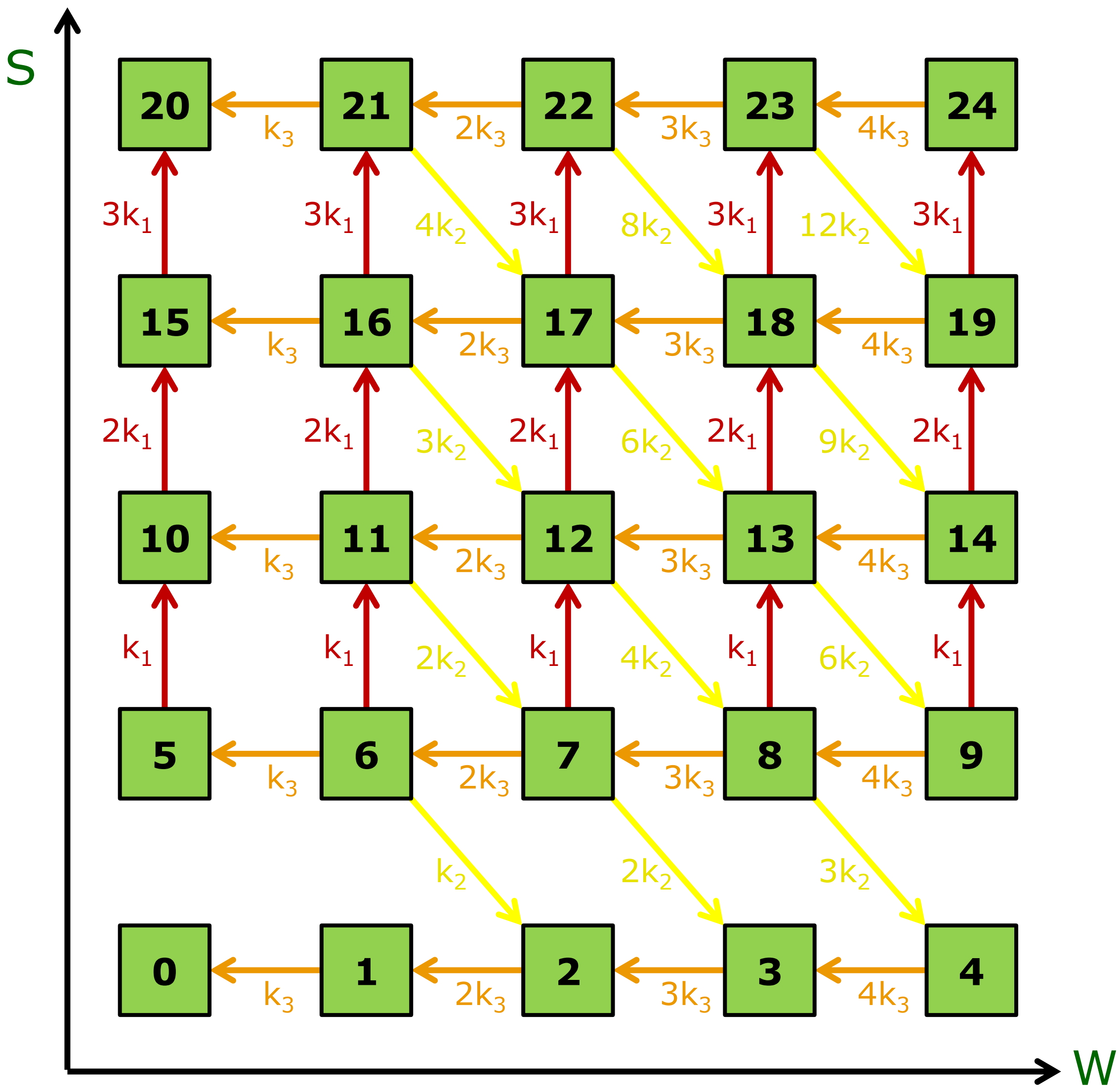
$$W \xrightarrow{k_3}$$

$$a_1 = k_1.[S]$$

$$a_2 = k_2.[W].[S]$$

$$a_3 = k_3.[W]$$

Biochemical system – Stochastic / CTMC / State space enumeration



$$S \xrightarrow{k_1} 2\,S$$

$$W + S \xrightarrow{k_2} 2\,W$$

$$W \xrightarrow{k_3}$$

$$a_1 = k_1.[S]$$

$$a_2 = k_2.[W].[S]$$

$$a_3 = k_3.[W]$$

Biochemical system – Stochastic / CTMC / Q matrix

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
0	0																								
1	k_3	$-\Sigma$																							
2		$2k_3$	$-\Sigma$																						
3			$3k_3$	$-\Sigma$																					
4				$4k_3$	$-\Sigma$																				
5						$-\Sigma$					k_1														
6			k_2			k_3	$-\Sigma$					k_1													
7				$2k_2$			$2k_3$	$-\Sigma$					k_1												
8					$3k_2$			$3k_3$	$-\Sigma$					k_1											
9									$4k_3$	$-\Sigma$					k_1										
10											$-\Sigma$					$2k_1$									
11								$2k_2$			k_3	$-\Sigma$					$2k_1$								
12									$4k_2$			$2k_3$	$-\Sigma$					$2k_1$							
13										$6k_2$			$3k_3$	$-\Sigma$					$2k_1$						
14														$4k_3$	$-\Sigma$					$2k_1$					
15																$-\Sigma$					$3k_1$				
16													$3k_2$			k_3	$-\Sigma$					$3k_1$			
17														$6k_2$			$2k_3$	$-\Sigma$					$3k_1$		
18															$9k_2$			$3k_3$	$-\Sigma$					$3k_1$	
19																			$4k_3$	$-\Sigma$					$3k_1$
20																					0				
21																		$4k_2$			k_3	$-\Sigma$			
22																			$8k_2$			$2k_3$	$-\Sigma$		
23																				$12k_2$			$3k_3$	$-\Sigma$	
24																								$4k_3$	$-\Sigma$

$$S \xrightarrow{k_1} 2\,S$$

$$W + S \xrightarrow{k_2} 2\,W$$

$$W \xrightarrow{k_3}$$

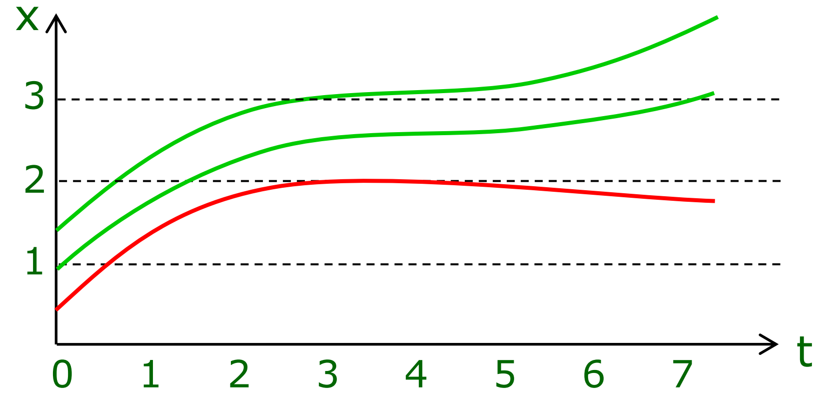
$$a_1 = k_1.[S]$$

$$a_2 = k_2.[W].[S]$$

$$a_3 = k_3.[W]$$

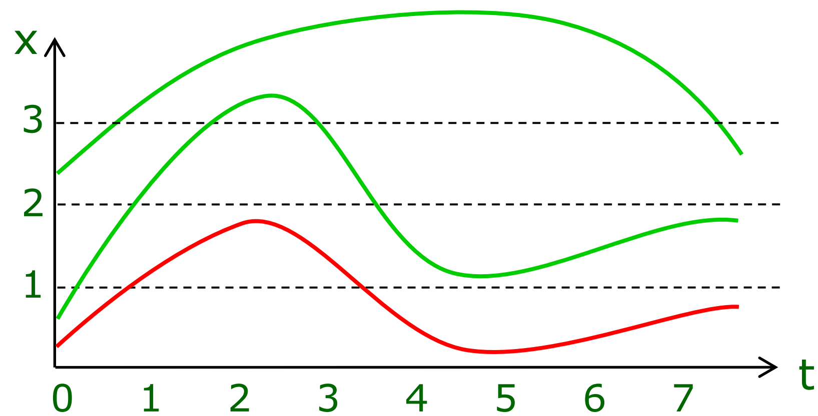
Signal Temporal Logic

$\varphi = a \mid\, !\varphi \mid \varphi \wedge \varphi \mid \varphi U^{[a,b]} \varphi \mid G^{[a,b]} \varphi \mid F^{[a,b]} \varphi$



Reachability

$F^{[0,7]}(x>3)$

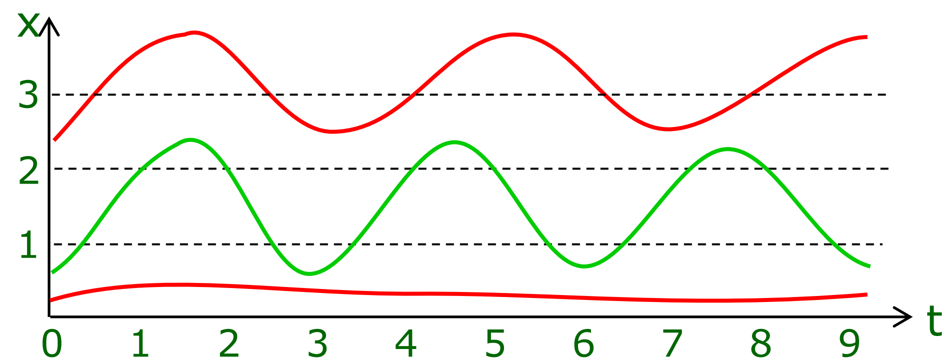


Response

$G^{[0,3]}((x<1) \Rightarrow F^{[0,2]}(x>3))$

Oscillation

$G^{[0,5]}(\ (x<1) \Rightarrow F^{[0,3]}(x>2) \wedge$
$(x>2) \Rightarrow F^{[0,3]}(x<1)\ )$



Continuous Stochastic Logic

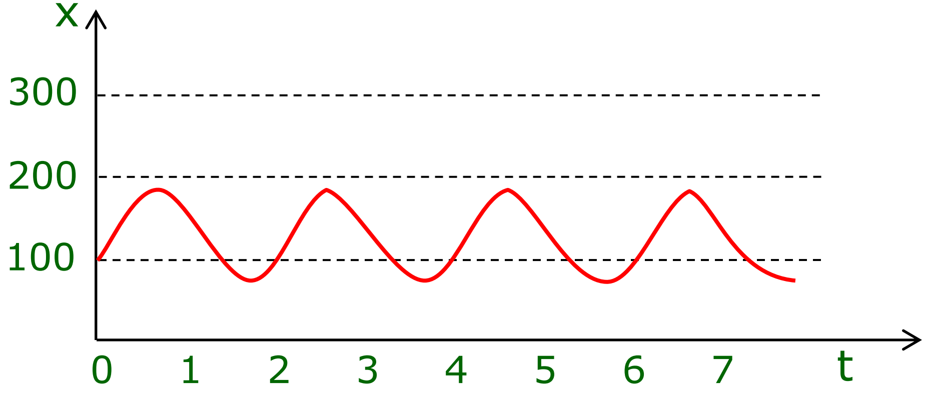
$\Phi = tt \mid a \mid !\Phi \mid \Phi \wedge \Phi \mid P_{\sim s}[\varphi] \mid S_{\sim s}[\varphi]$ $\sim \in \{<, \leq, \geq, >\}, s \in [0,1]$

$\varphi = X\Phi \mid \Phi U^{[a,b]}\Phi$ $0 \leq a \leq b \in \mathbb{R}$

$F^{[a,b]}\Phi = tt\ U^{[a,b]}\Phi$ $G^{[a,b]}\Phi = !\ F^{[a,b]}\ !\Phi$

Reachability

$P_{>0.2}\ [F^{[0,7]}(x > 300)]$



Continuous Stochastic Logic

$\Phi = tt \mid a \mid !\Phi \mid \Phi \wedge \Phi \mid P_{\sim s}[\varphi] \mid S_{\sim s}[\varphi]$ $\sim \in \{<, \leq, \geq, >\}, s \in [0,1]$

$\varphi = X\Phi \mid \Phi U^{[a,b]}\Phi$ $0 \leq a \leq b \in \mathbb{R}$

$F^{[a,b]}\Phi = tt\, U^{[a,b]}\Phi$ $G^{[a,b]}\Phi = !\, F^{[a,b]}\, !\Phi$

Reachability

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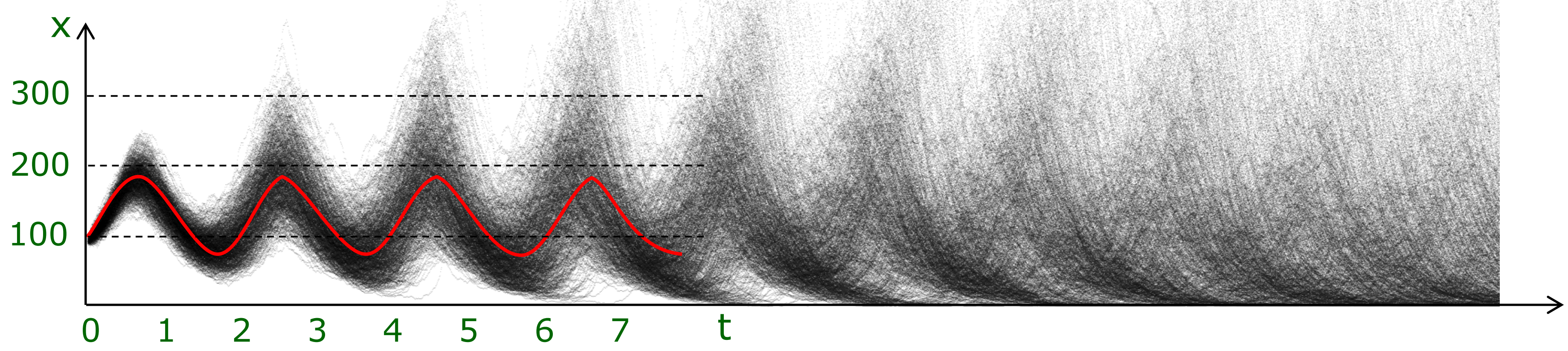
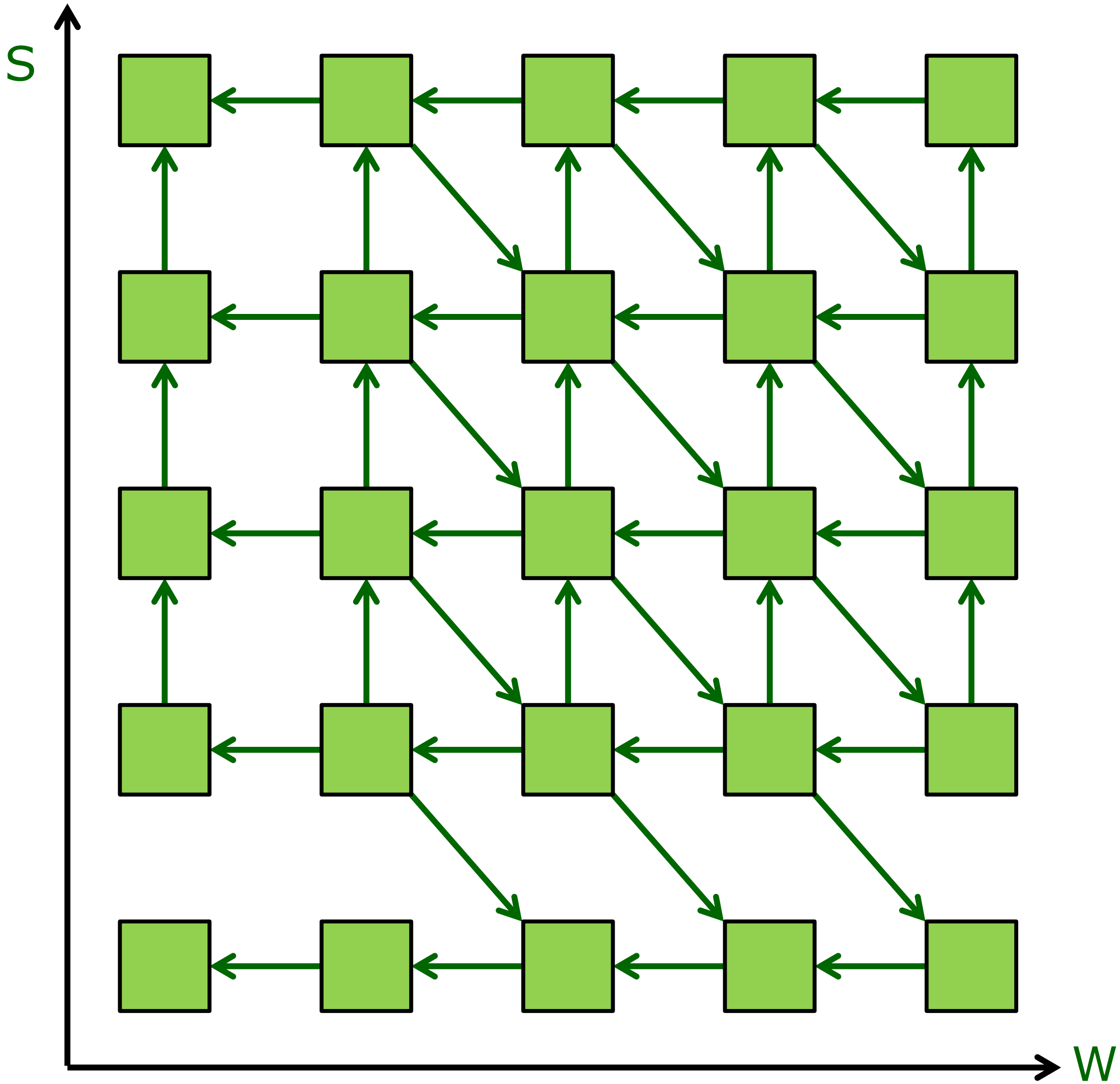


Perturbations



System

$$S \xrightarrow{k_1} 2\,S$$

$$W + S \xrightarrow{k_2} 2\,W$$

$$W \xrightarrow{k_3}$$

$$a_1 = f(k_1.[S],t)$$

$$a_2 = f(k_2.[W].[S],t)$$

$$a_3 = f(k_3.[W],t)$$

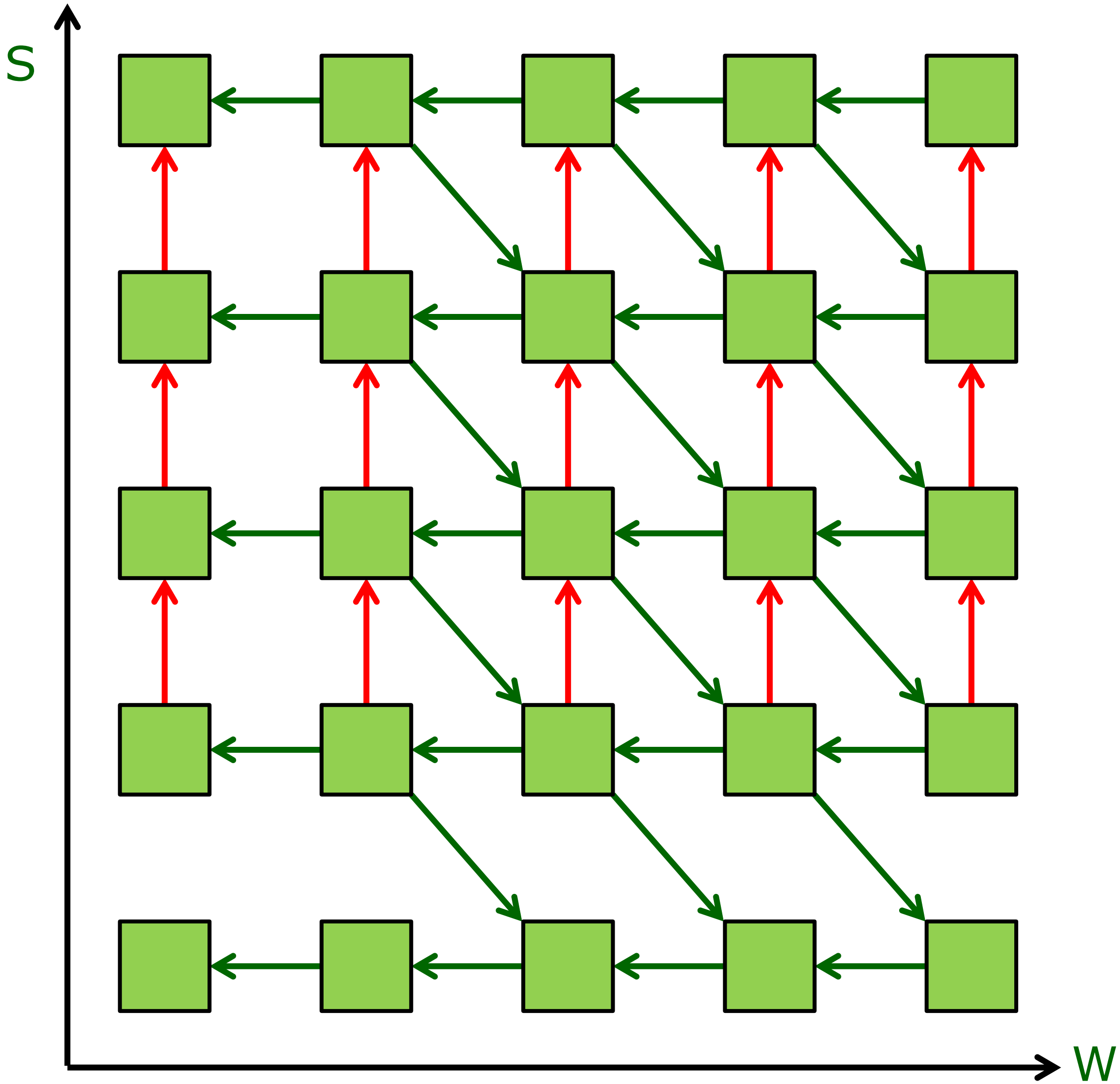
Initial conditions

$S = 2,\ W = 3$

Property

$$P_{>0.2}\,[F^{[0,7]}(x > 300)]$$

Perturbations / kinetic parameter



System

$S \xrightarrow{k_1} 2\,S$

$W + S \xrightarrow{k_2} 2\,W$

$W \xrightarrow{k_3}$

$a_1 = f(k_1.[S],t)$
$a_2 = f(k_2.[W].[S],t)$
$a_3 = f(k_3.[W],t)$

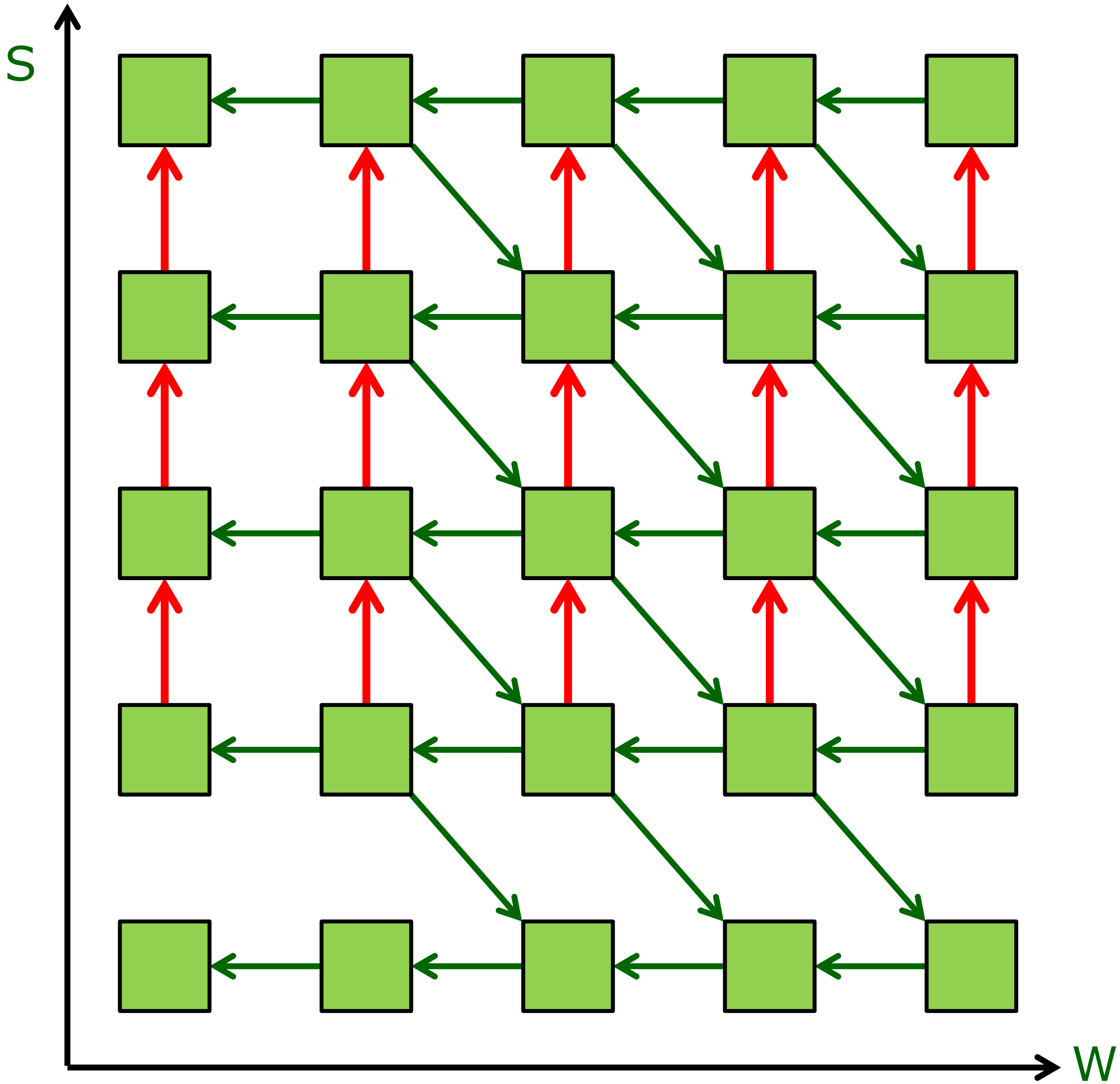
Initial conditions

S = 2, W = 3

Property

$P_{>0.2}\,[F^{[0,7]}(x > 300)]$

Perturbations / kinetic parameter



System

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Initial conditions

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Property

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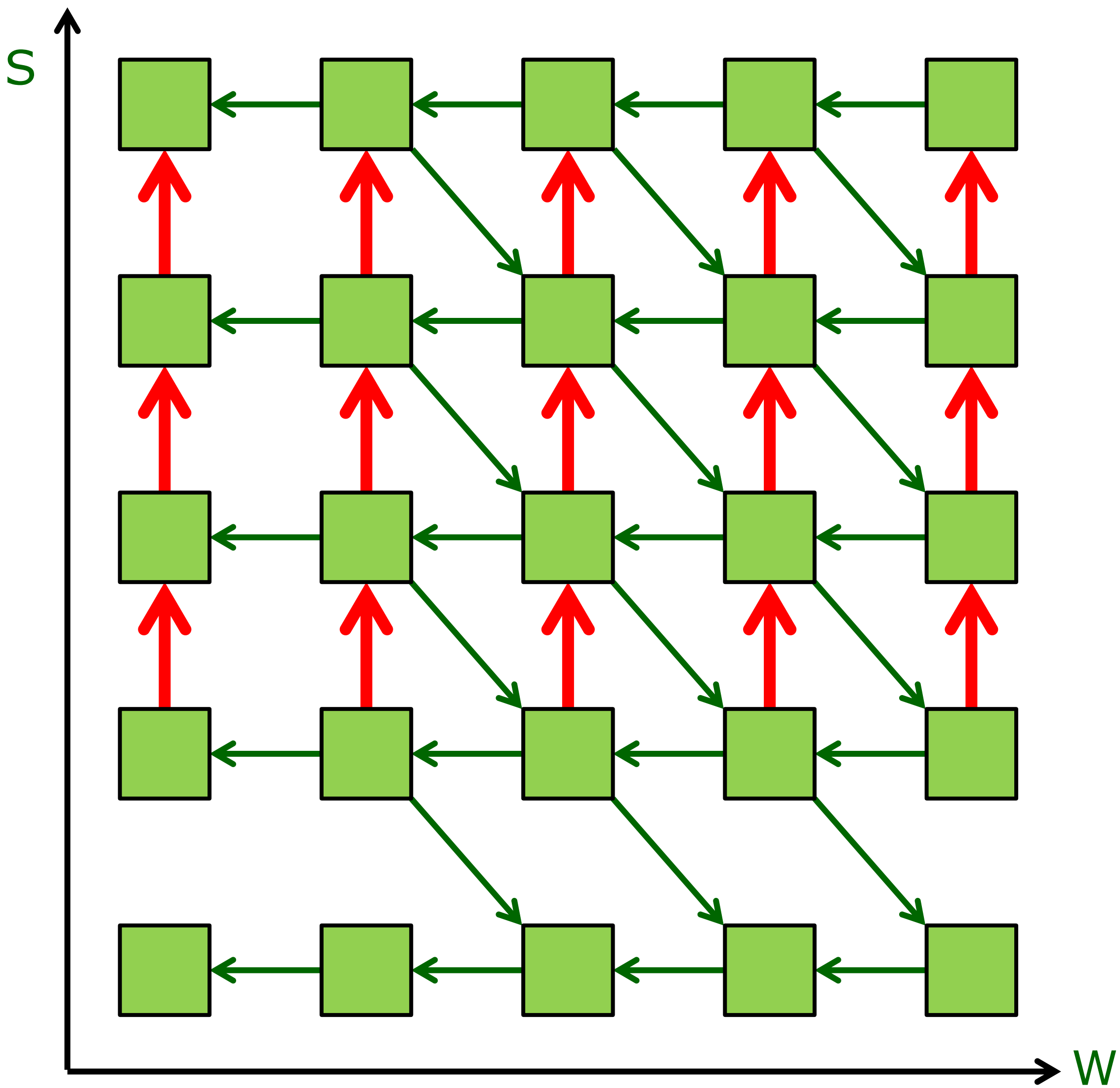
Perturbations / kinetic parameter



System

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$$W \xrightarrow{k_3}$$

$$a_1 = f(k_1.[S],t)$$
$$a_2 = f(k_2.[W].[S],t)$$
$$a_3 = f(k_3.[W],t)$$

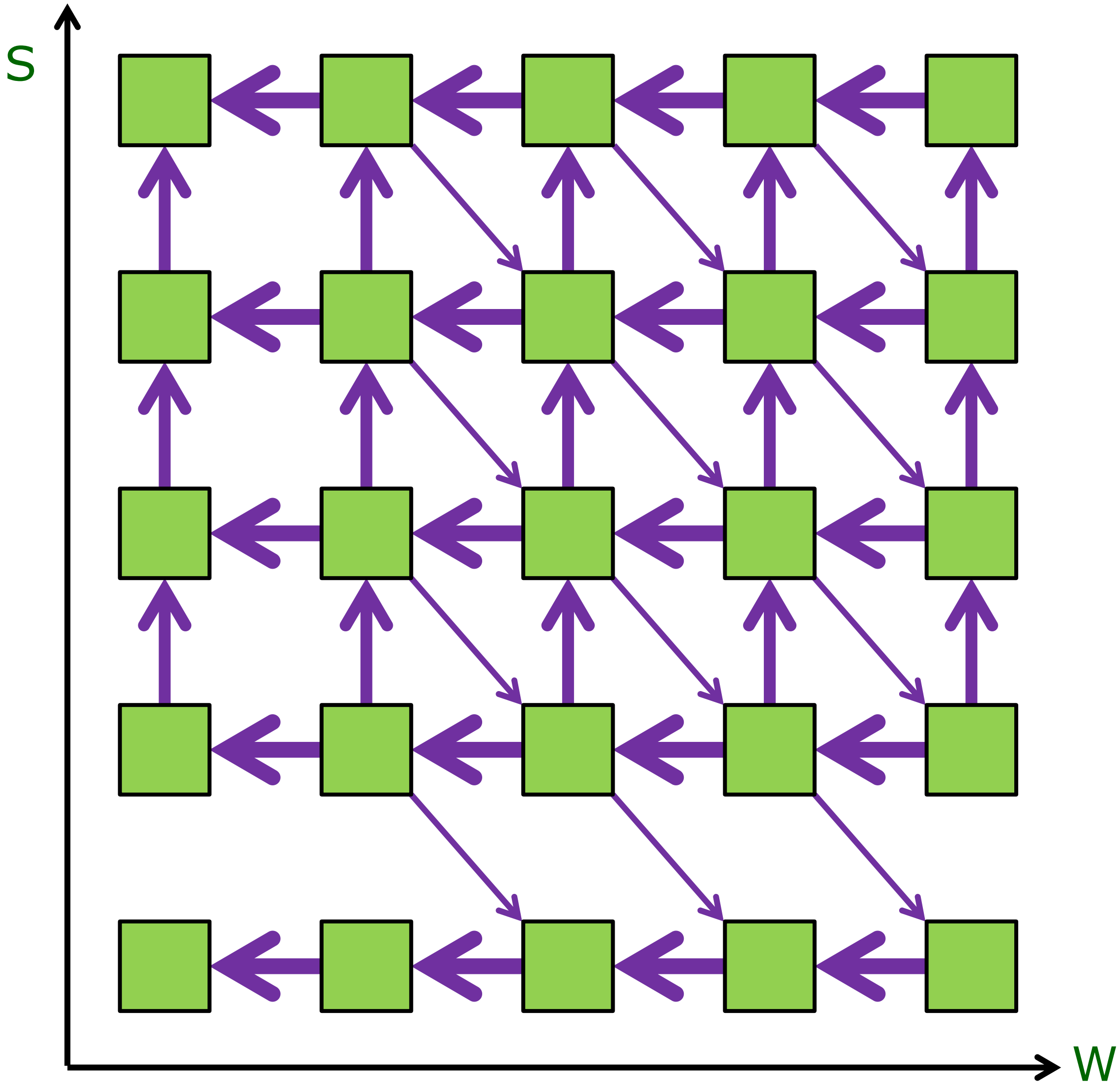
Initial conditions

$S = 2,\ W = 3$

Property

$$P_{>0.2}\,[F^{[0,7]}(x > 300)]$$

Perturbations / external parameter



System

$$S \xrightarrow{k_1} 2\,S$$

$$W + S \xrightarrow{k_2} 2\,W$$

$$W \xrightarrow{k_3}$$

$$a_1 = f(k_1.[S],t)$$

$$a_2 = f(k_2.[W].[S],t)$$

$$a_3 = f(k_3.[W],t)$$

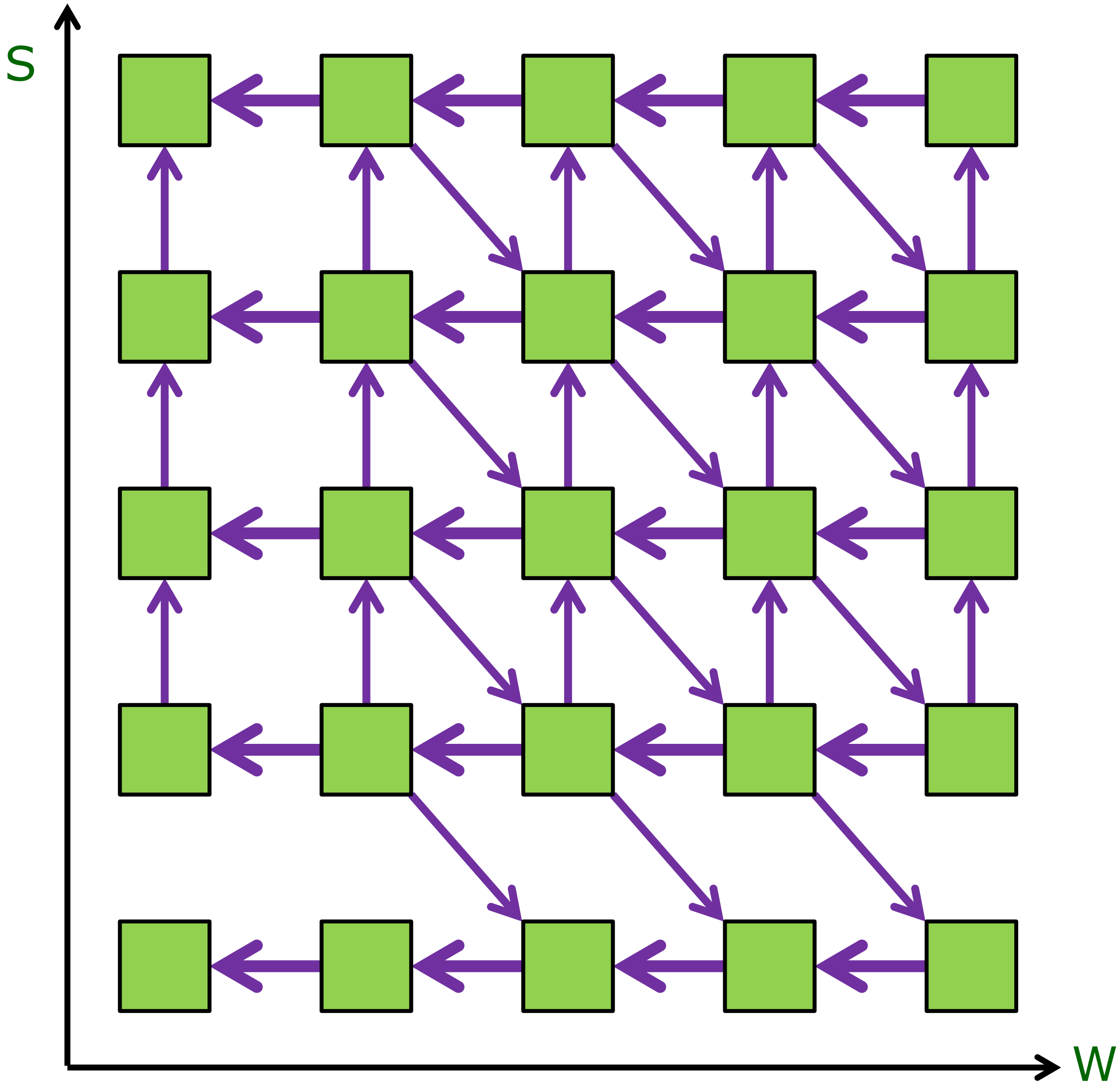
Initial conditions

$S = 2,\ W = 3$

Property

$$P_{>0.2}\,[F^{[0,7]}(x > 300)]$$

Perturbations / external parameter



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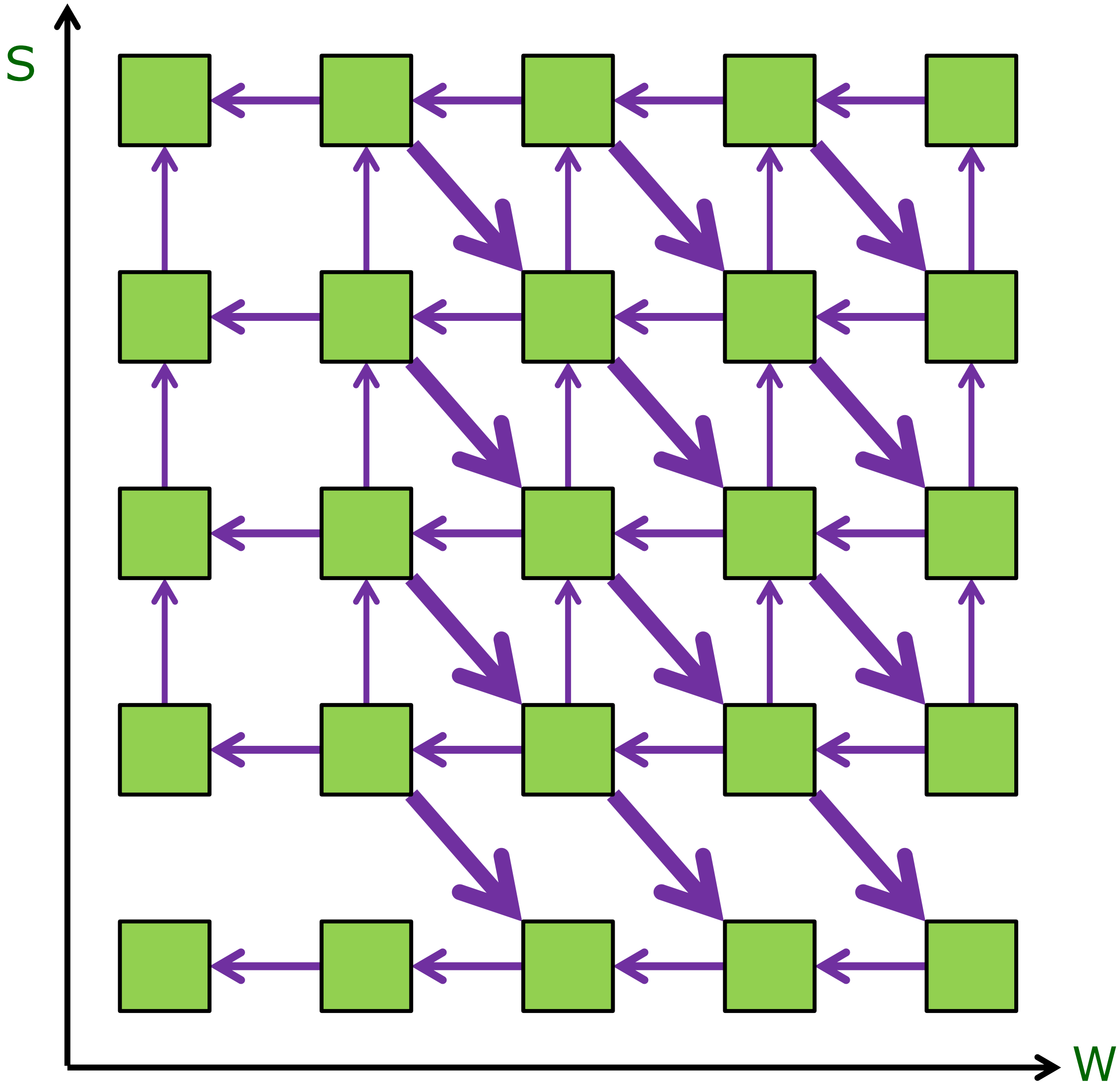

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Initial conditions

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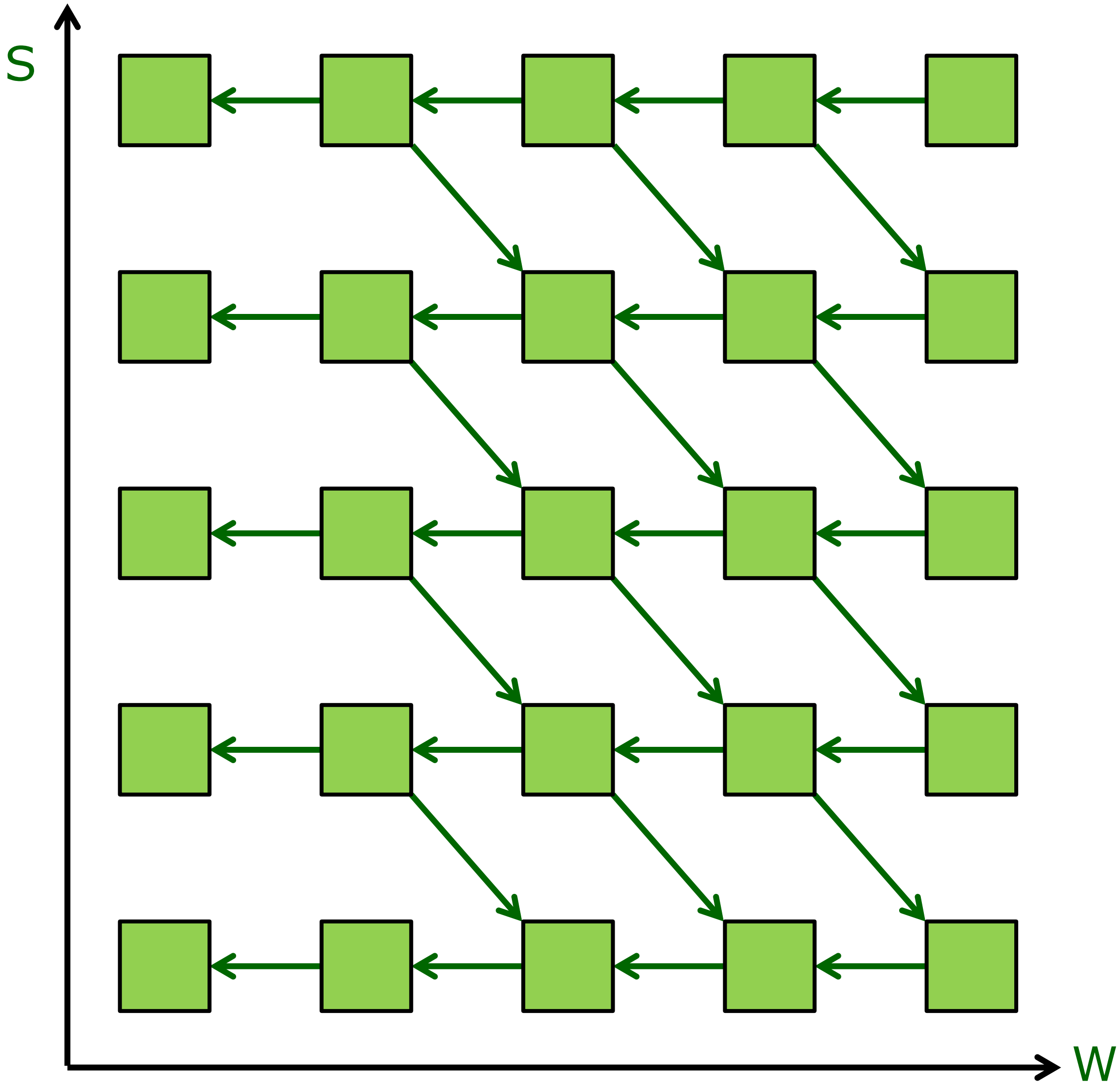
Property

$$P_{>0.2}\,[F^{[0,7]}(x > 300)]$$

Perturbations / system structure



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$W + S \xrightarrow{k_2} 2\,W$

$W \xrightarrow{k_3}$

$a_1 = f(k_1.[S],t)$
$a_2 = f(k_2.[W].[S],t)$
$a_3 = f(k_3.[W],t)$

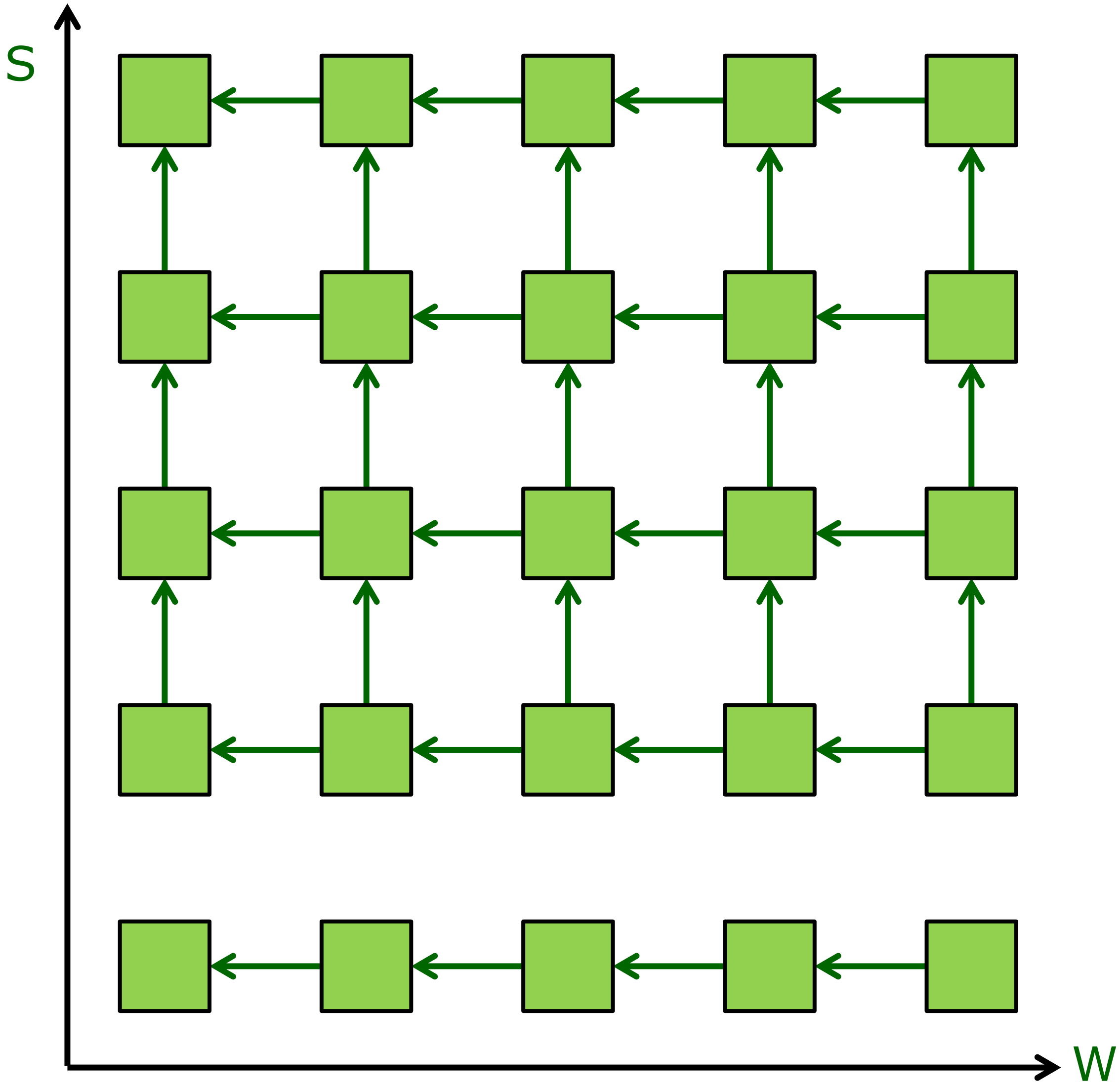
Initial conditions

$S = 2,\ W = 3$

Property

$P_{>0.2}\,[F^{[0,7]}(x > 300)]$

Perturbations / system structure



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Initial conditions

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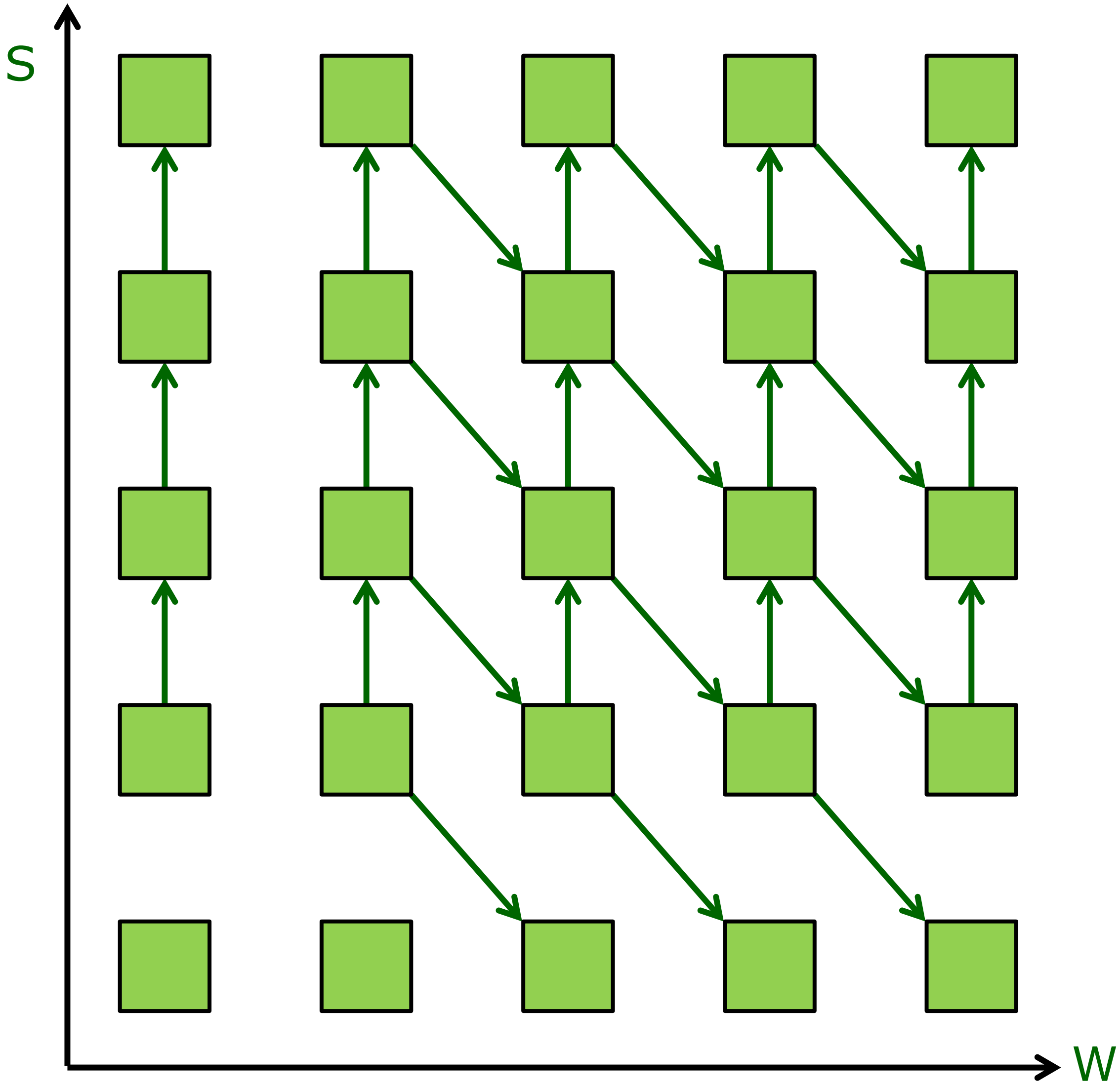

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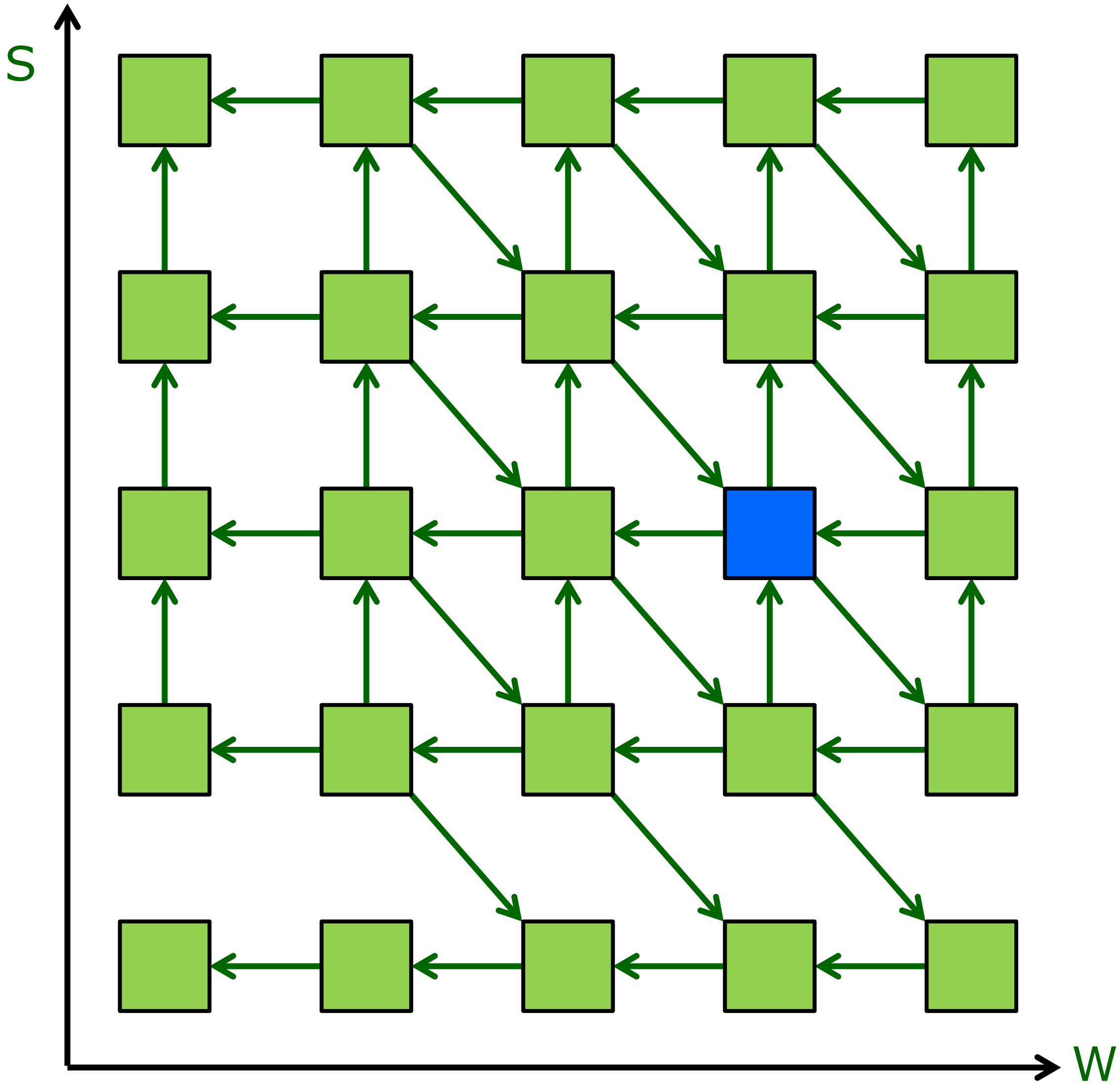

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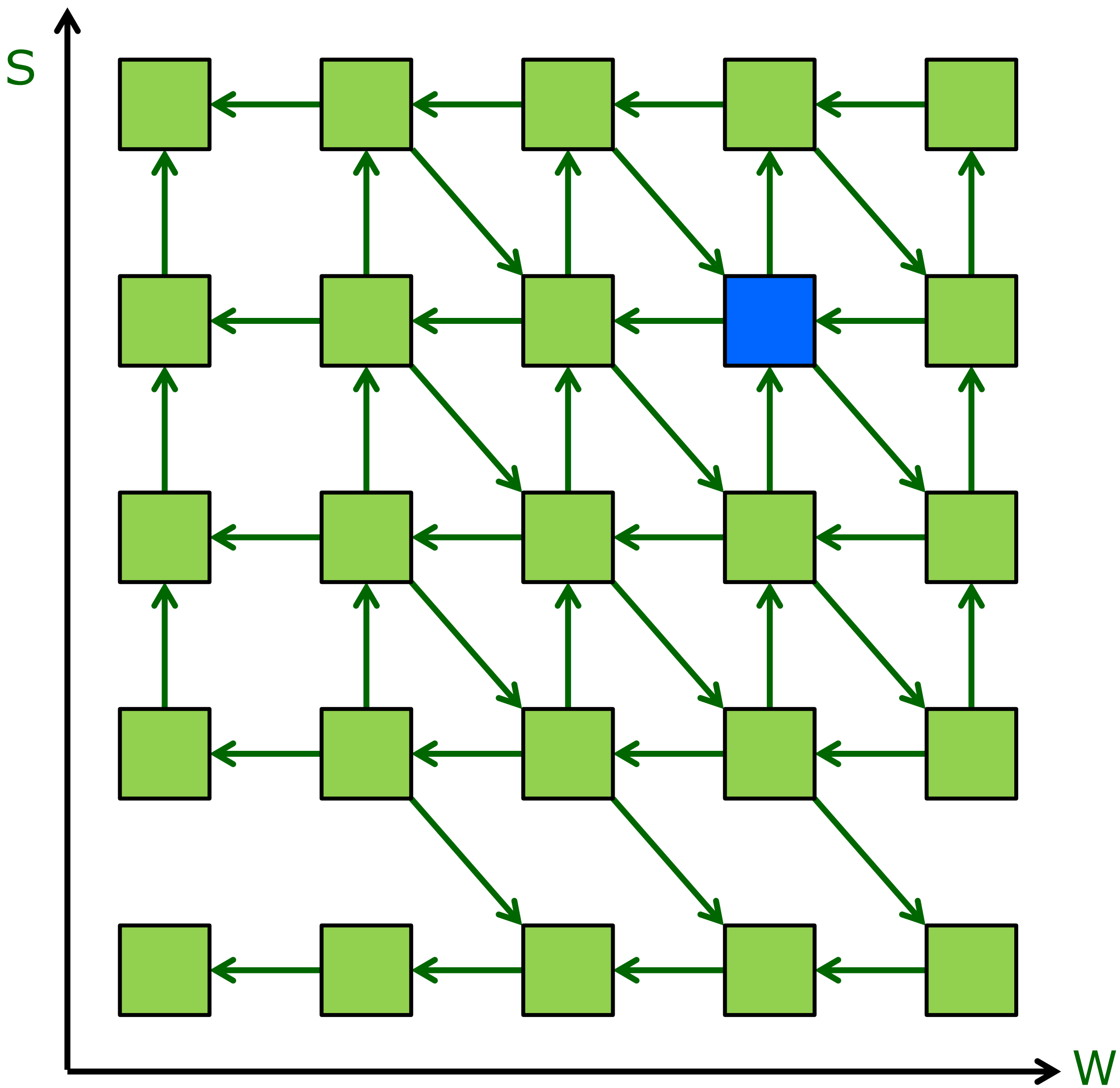

System

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$$a_1 = f(k_1.[S],t)$$

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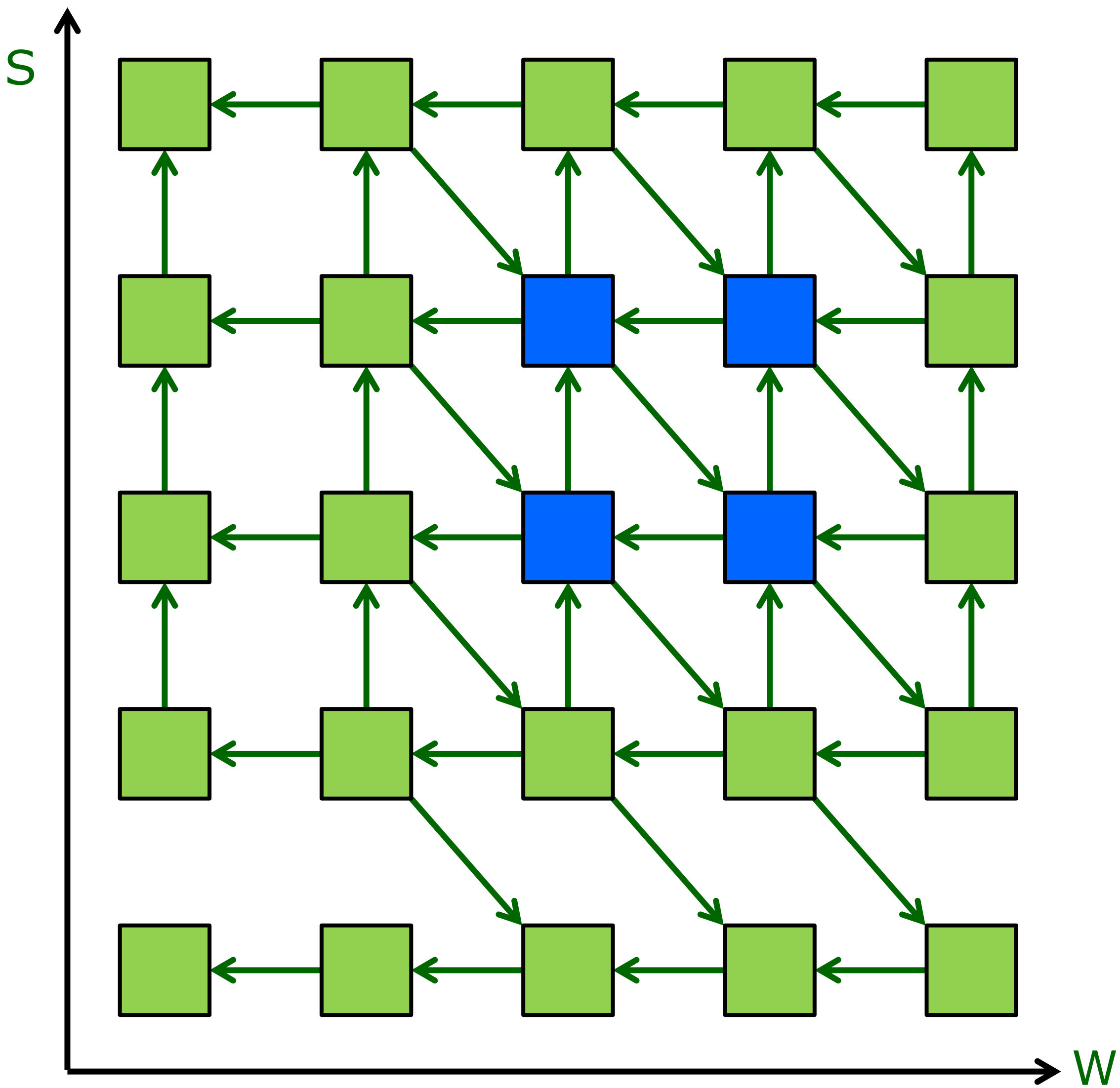
$$a_3 = f(k_3.[W],t)$$

Initial conditions

S = 3, W = 3

Property

$$P_{>0.2}\,[F^{[0,7]}(x > 300)]$$



System

$$S \xrightarrow{k_1} 2\,S$$

$$W + S \xrightarrow{k_2} 2\,W$$

$$W \xrightarrow{k_3}$$

$$a_1 = f(k_1.[S],t)$$

$$a_2 = f(k_2.[W].[S],t)$$

$$a_3 = f(k_3.[W],t)$$

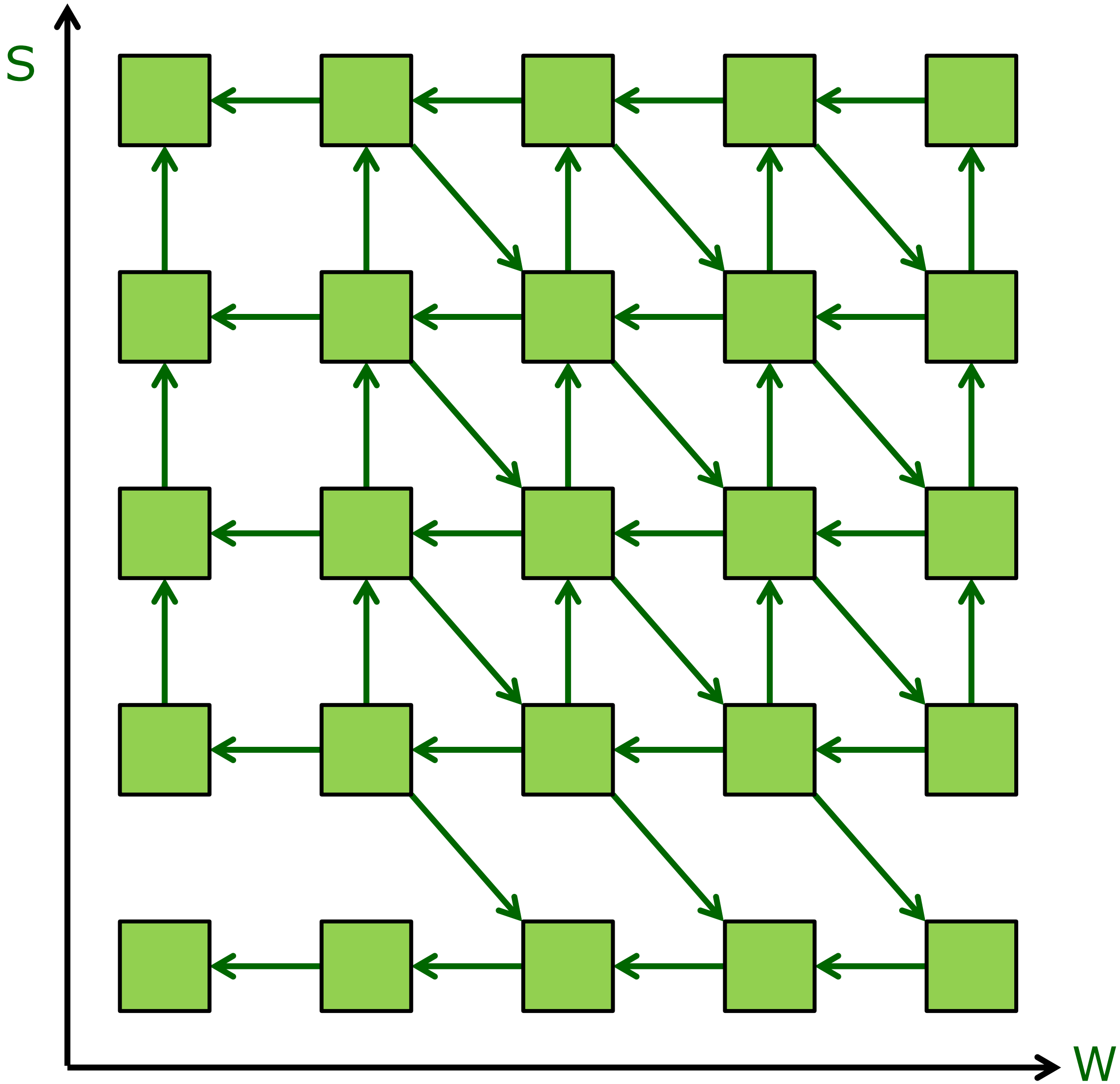
Initial conditions

$S \in [2,3]$ $W \in [2,3]$

Property

$P_{>0.2}\,[F^{[0,7]}(x > 300)]$

Perturbations / property



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$$W \xrightarrow{k_3}$$

$$a_1 = f(k_1.[S],t)$$

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$$a_3 = f(k_3.[W],t)$$

Initial conditions

S = 2, W = 3

Property

$$P_{>0.2}\,[F^{[0,7]}(x > 300)]$$

What is Robustness?

Robustness is the ability of a system to maintain its property against internal and external perturbations.

"Kitano, 2004"

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Robustness is the ability of a system to maintain its property against internal and external perturbations.

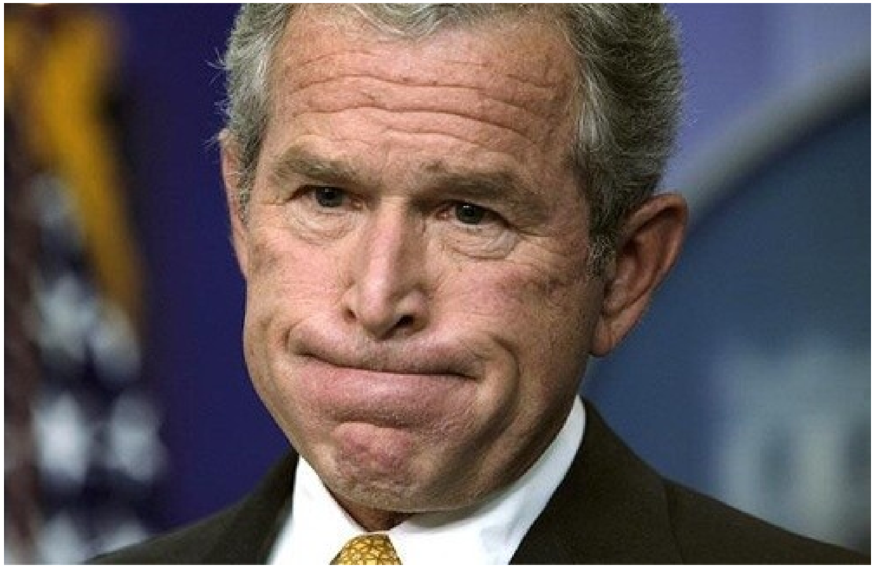
"Kitano, 2004"

$$R^{S}_{\Phi,\mathbf{P}} \overset{def}{=} \int_{\mathbf{P}} \psi(p) D^{S}_{\Phi}(p)\,dp$$

What is Robustness good for?

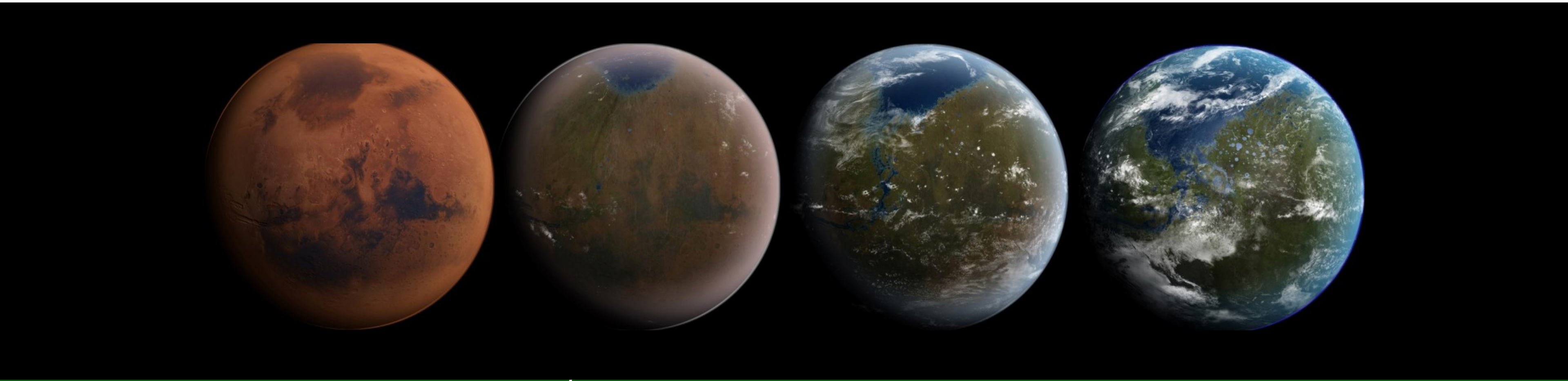

To get a bigger picture

What is Robustness good for?



Comparing systems

98.8% common DNA



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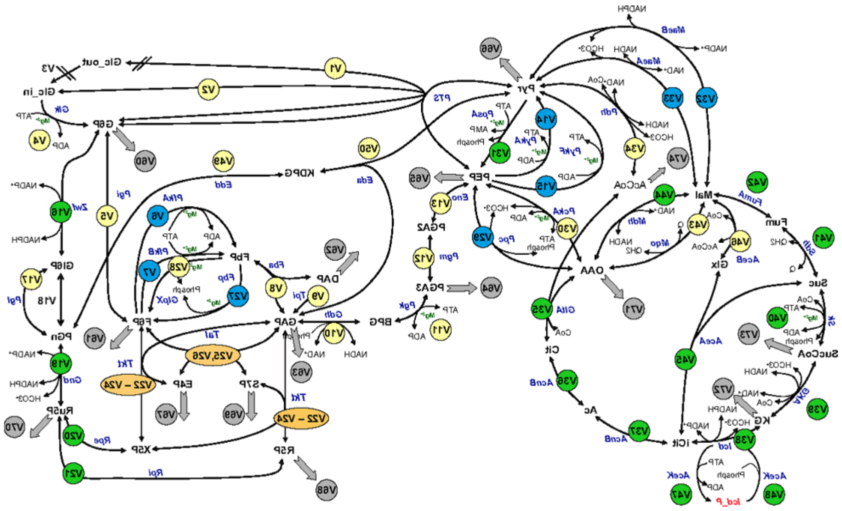
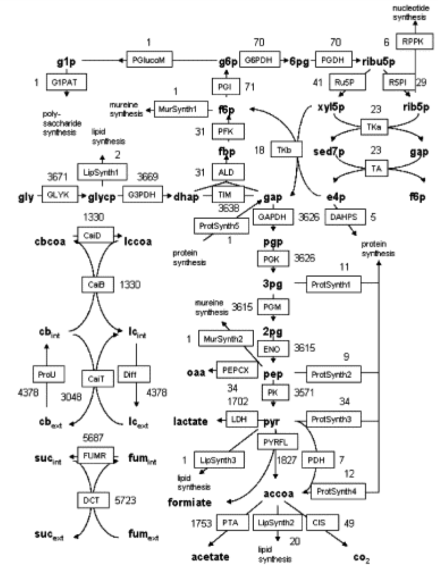
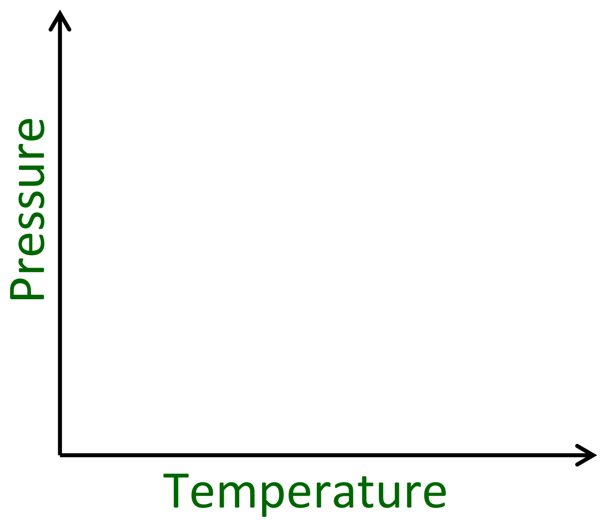
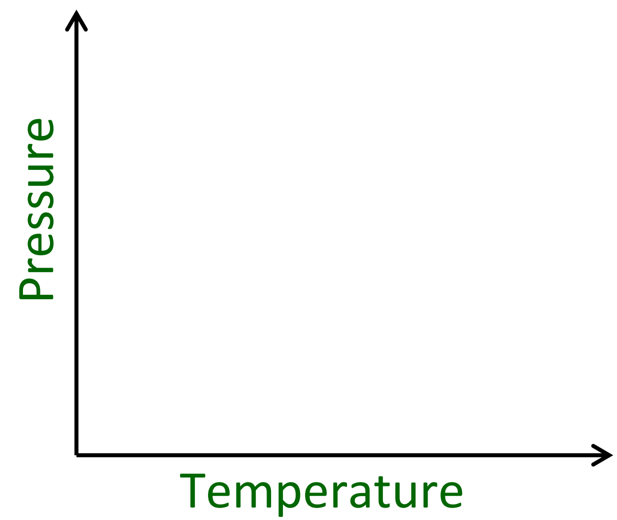




$$D_{\Phi}^{S}(p)$$

- = 0.0
- > 0.2
- > 0.4
- > 0.6
- > 0.8





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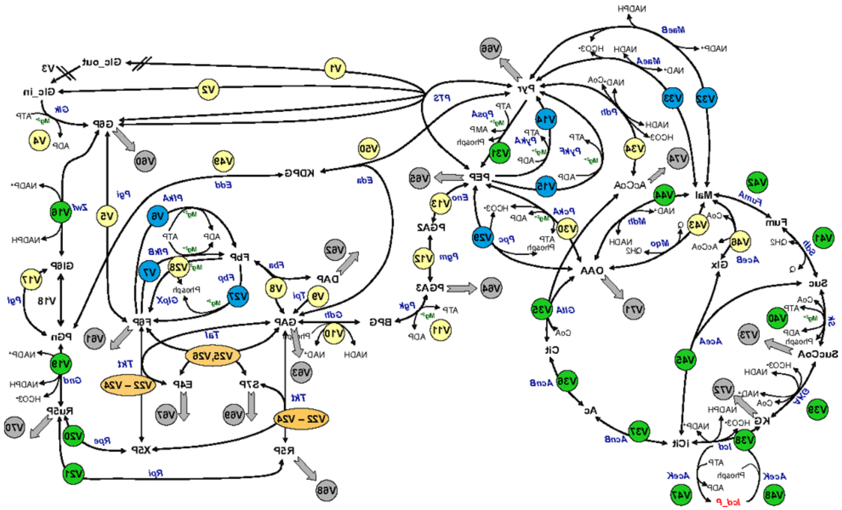
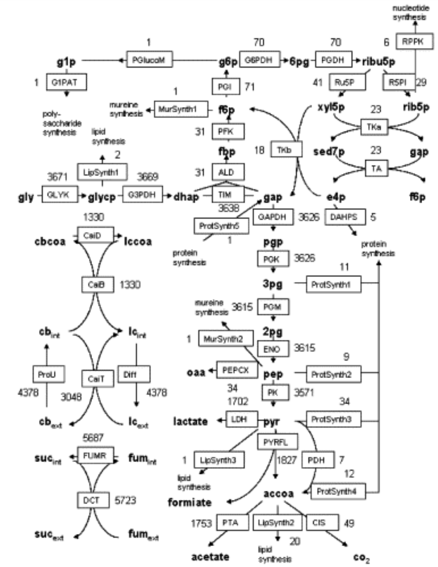
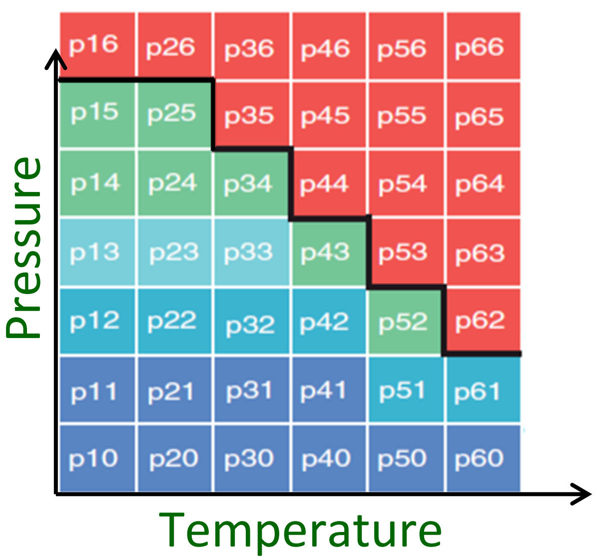






$$D^{S}_{\Phi}(p)$$

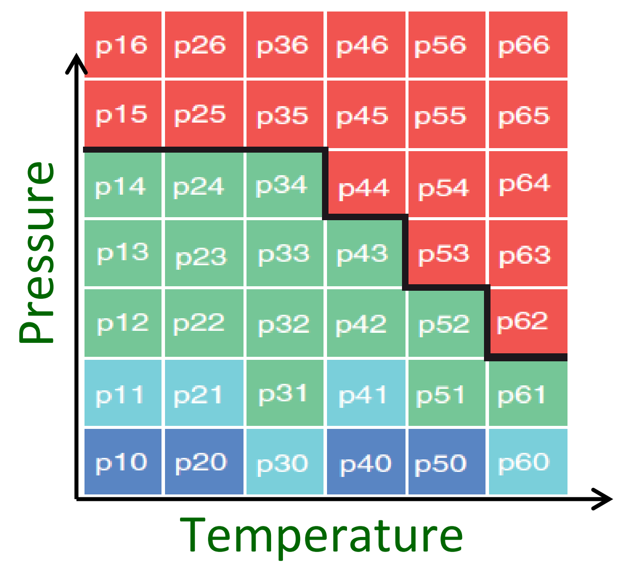
= 0.0

> 0.2

> 0.4

> 0.6

> 0.8



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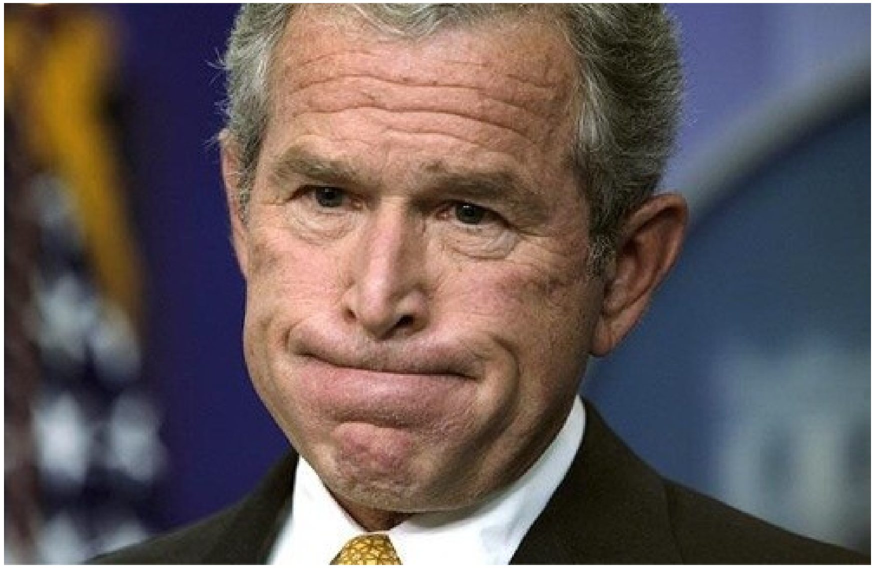
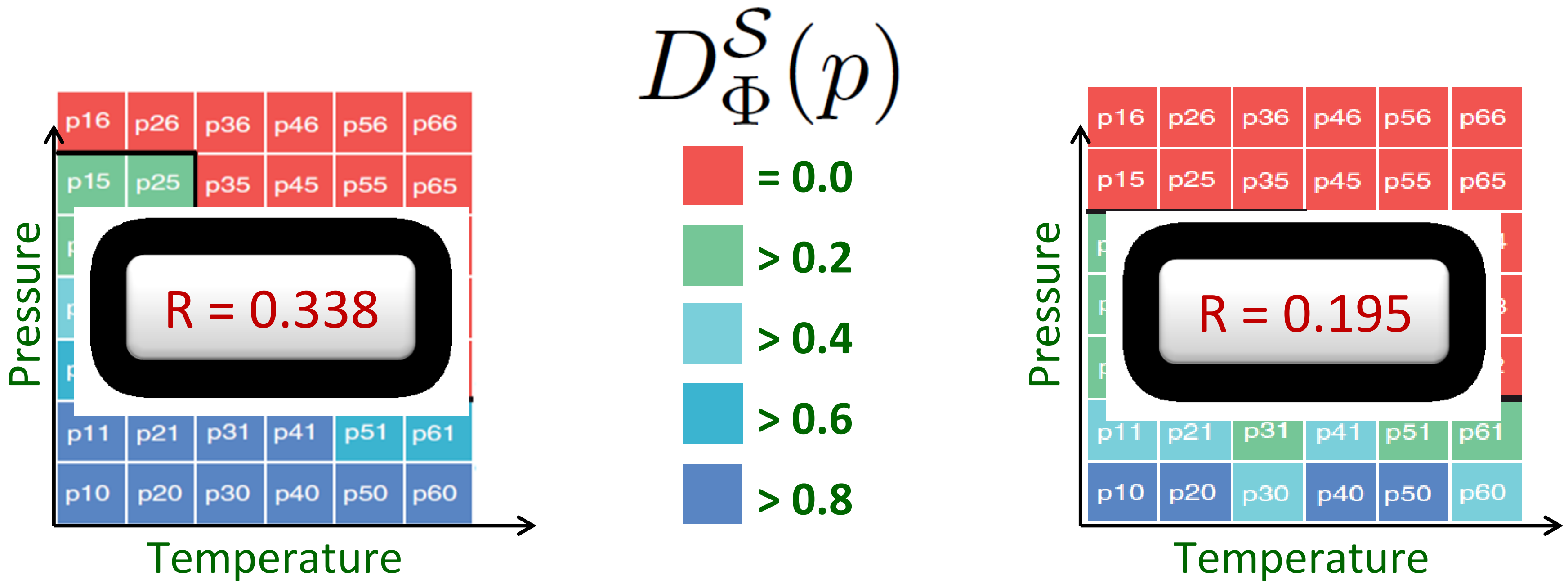
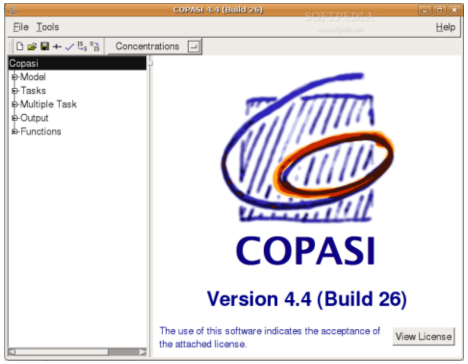
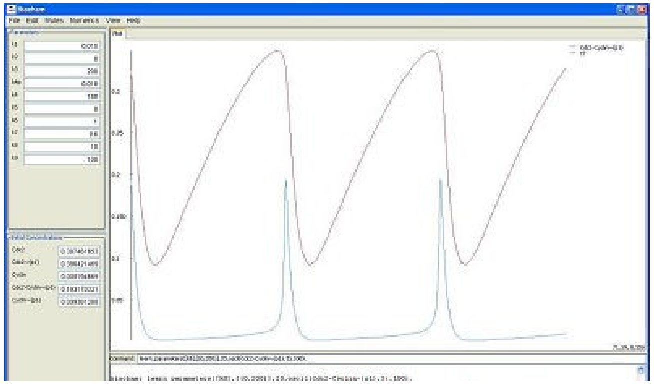




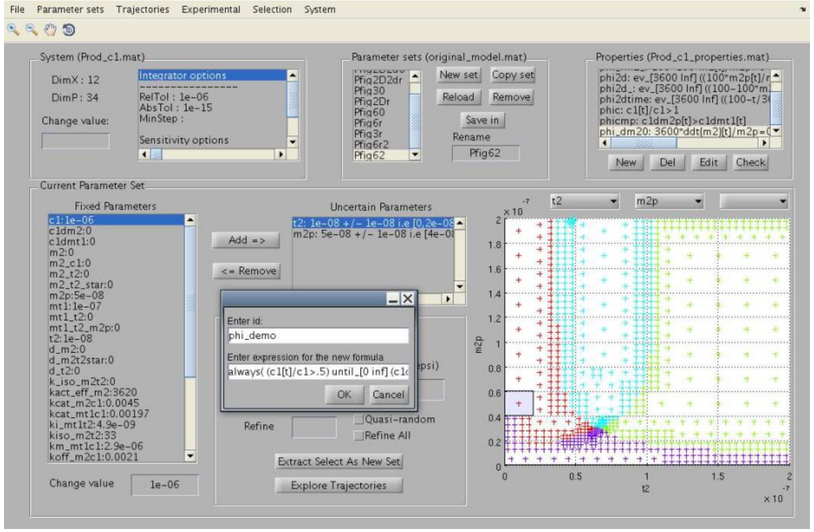
State of the art – Robustness for Deterministic ODEs



COPASI (S. Hoops et. al. 2006.)

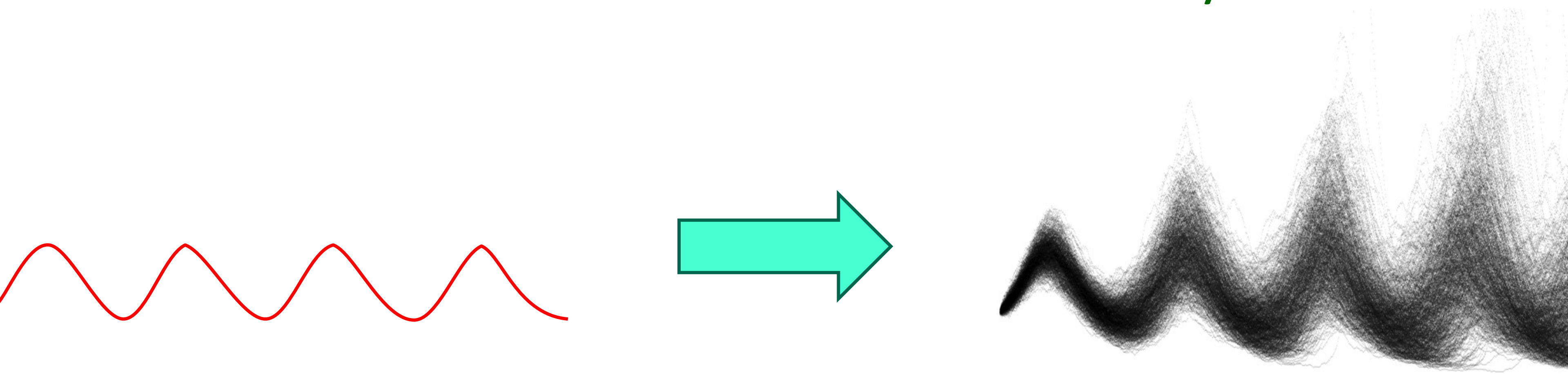


BioCham (F. Fages et. al. 2004)



Breach (A. Donzé and O. Maler, 2010)

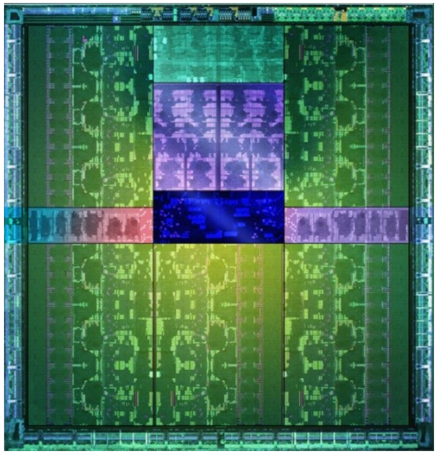
Definition of Robustness for Stochastic Systems



Efficient computational algorithms

$$\sum_{i=L_\epsilon}^{R_\epsilon} \gamma_{i,q\cdot t} \cdot \pi^{\mathcal{C},\bar{s},0} \cdot \left(\mathbf{Q}^{\mathsf{unif}(\mathcal{C})}\right)^i$$

	0	1	2	3	4	5	6	7	8	9	10	11	12
0	0												
1	k_3	-Σ											
2		$2k_3$	-Σ										
3			$3k_3$	-Σ									
4				$4k_3$	-Σ								
5						-Σ					k_1		
6			k_2			k_3	-Σ					k_1	
7				$2k_2$			$2k_3$	-Σ					k_1
8					$3k_2$			$3k_3$	-Σ				
9									$4k_3$	-Σ			
10											-Σ		
11								$2k_2$			k_3	-Σ	
12									$4k_2$			$2k_3$	-Σ

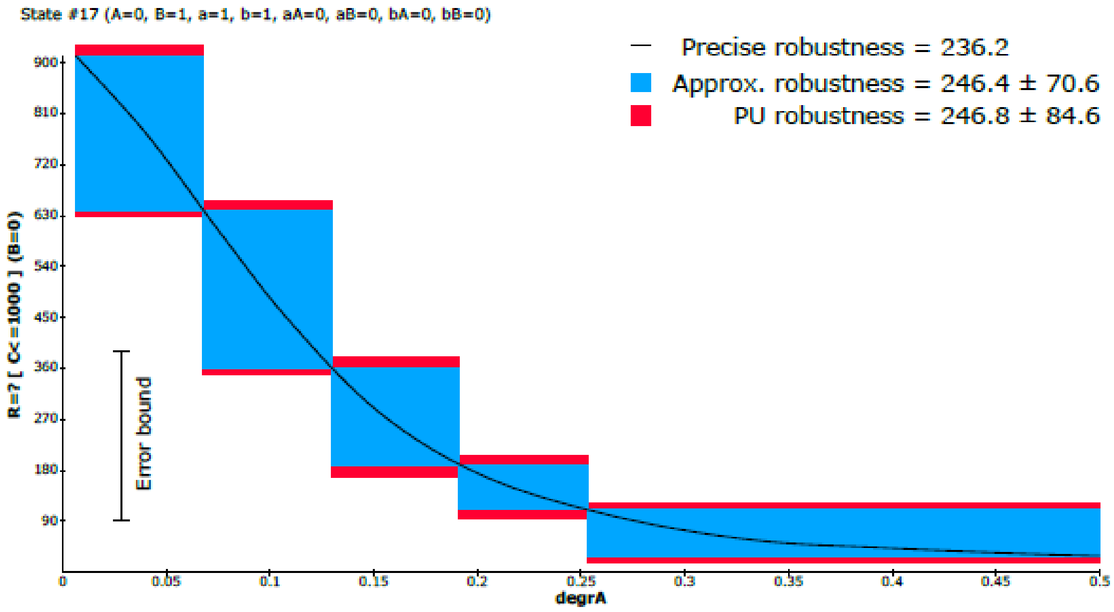


Full CSL

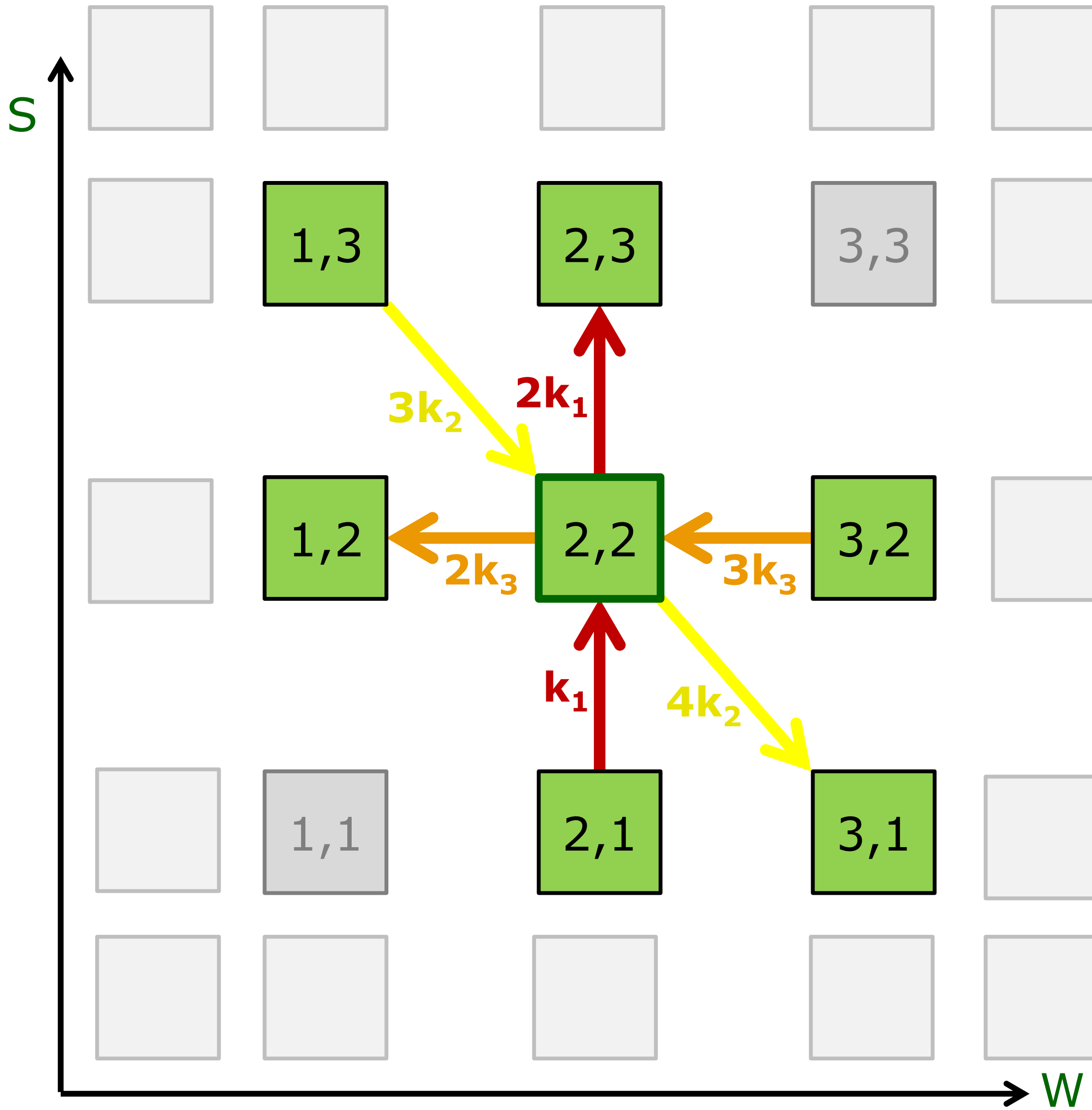
$$\Phi ::= \mathsf{true} \mid a \mid \neg\Phi \mid \Phi \wedge \Phi \mid \mathsf{P}_{\sim p}[\phi] \mid \mathsf{S}_{\sim p}[\Phi]$$
$$\phi ::= \mathsf{X}\ \Phi \mid \Phi\ \mathsf{U}^{I}\ \Phi$$

Bounded time CSL

$$\Phi ::= \mathsf{true} \mid a \mid \neg\Phi \mid \Phi \wedge \Phi \mid \mathsf{P}_{\sim p}[\phi]$$
$$\phi ::= \mathsf{X}\ \Phi \mid \Phi\ \mathsf{U}^{I}\ \Phi$$



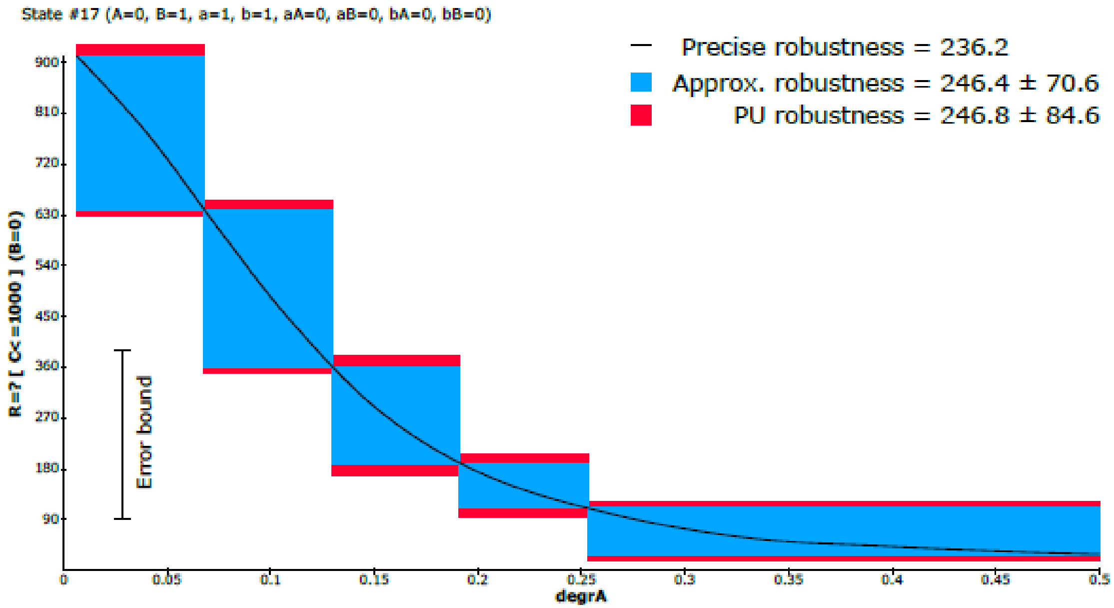
Preliminary results

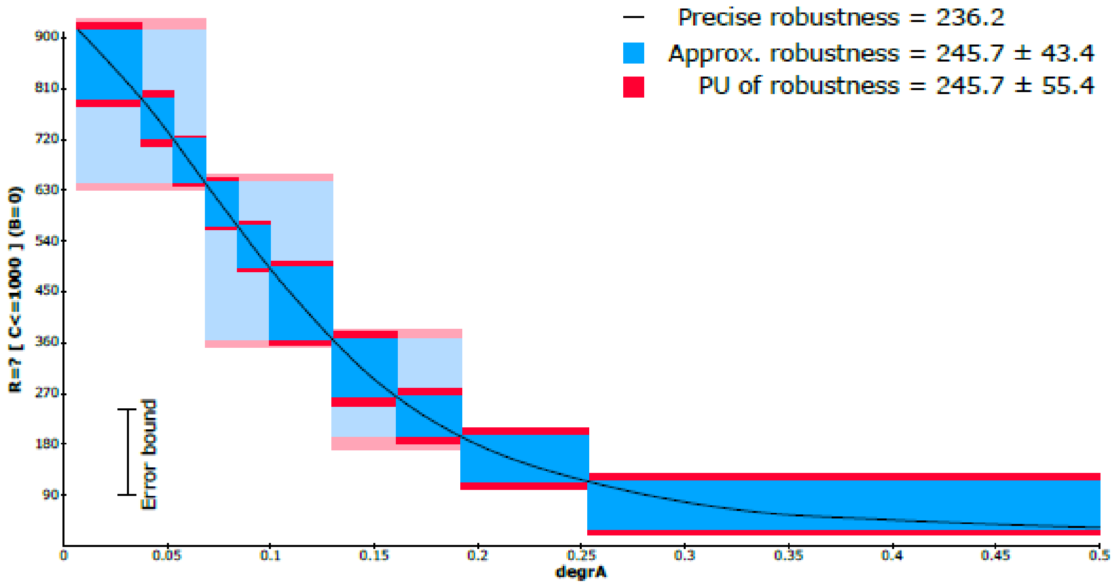


Local minimum

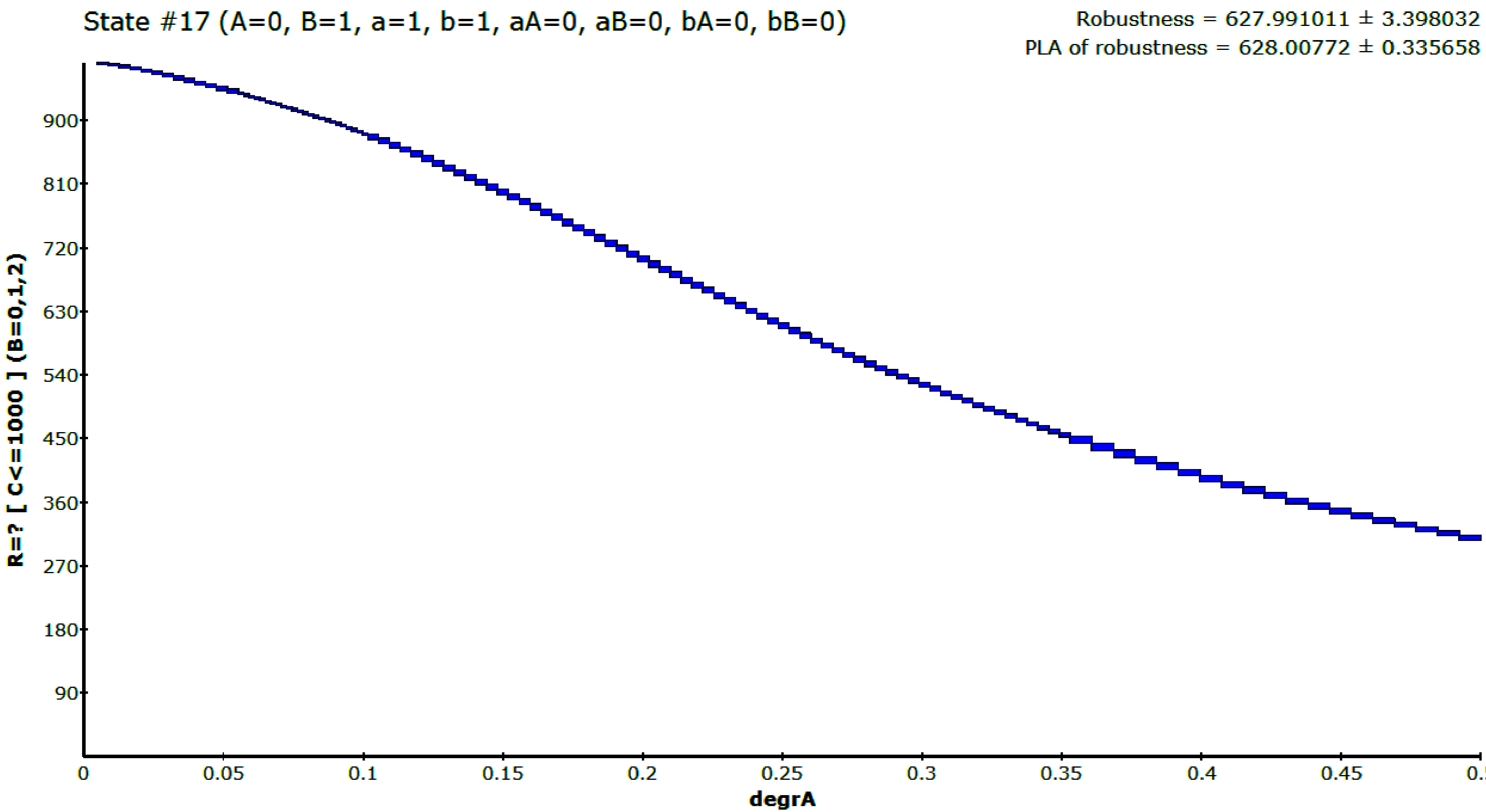
Local maximum

Preliminary results / Error control

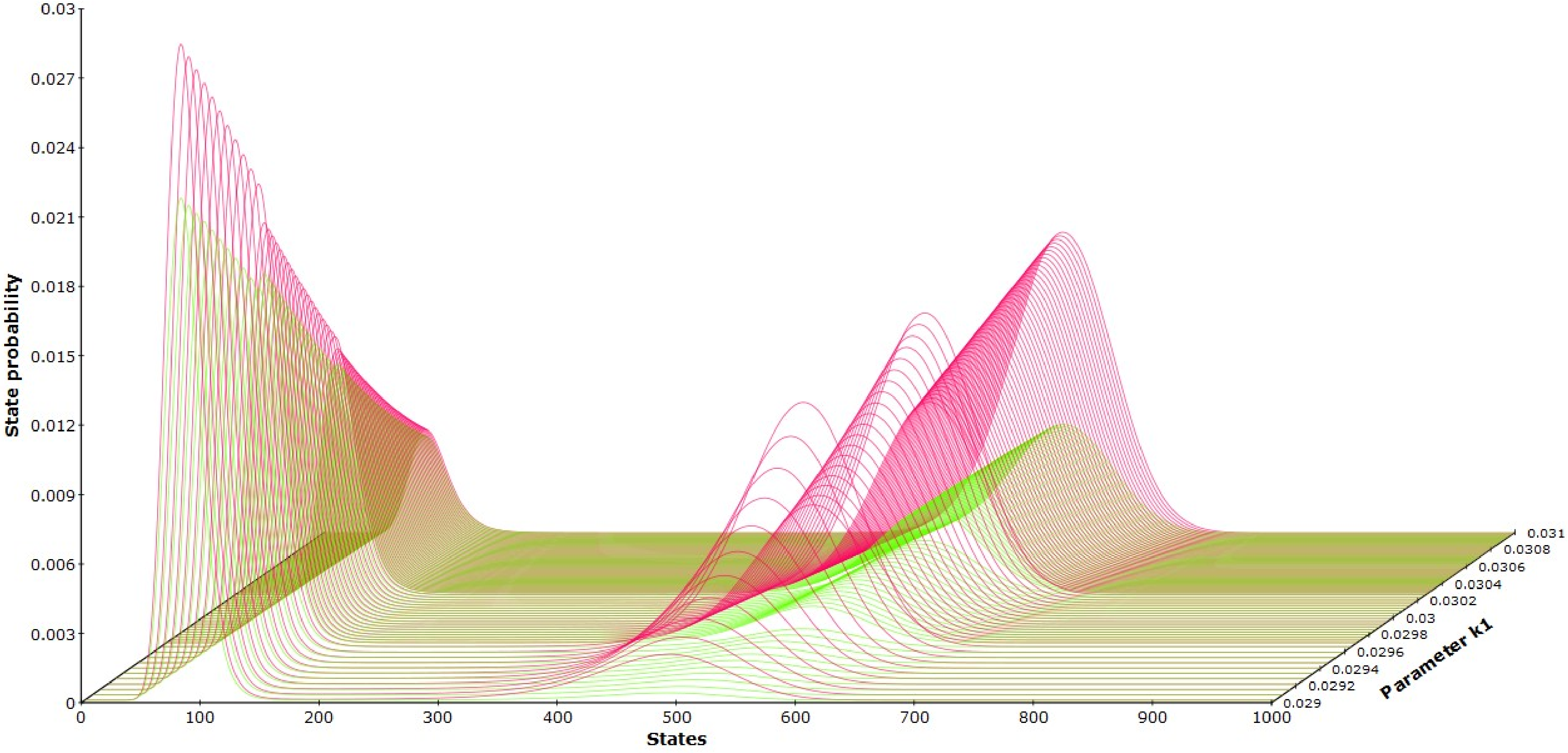




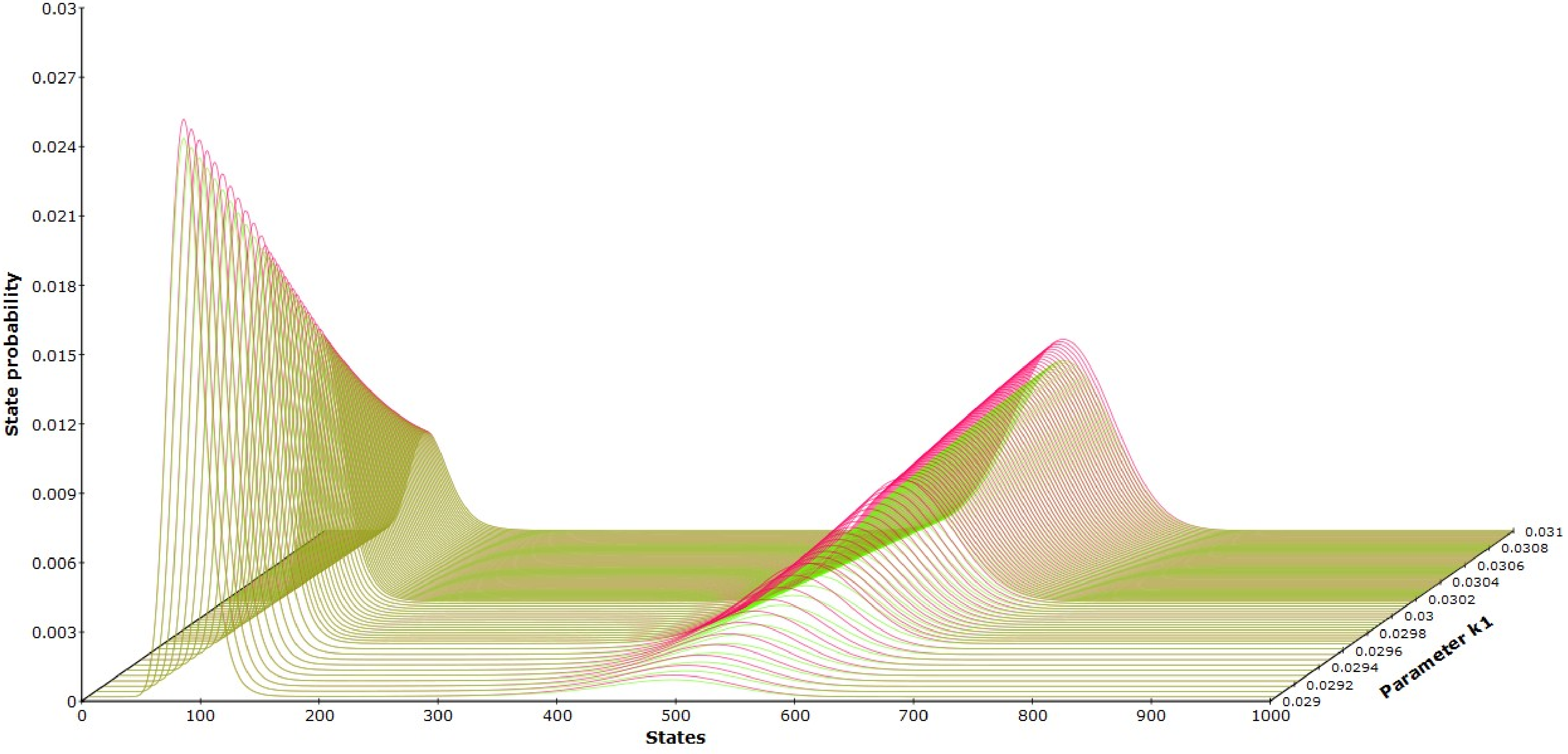
Preliminary results / 1D parameter space refinement



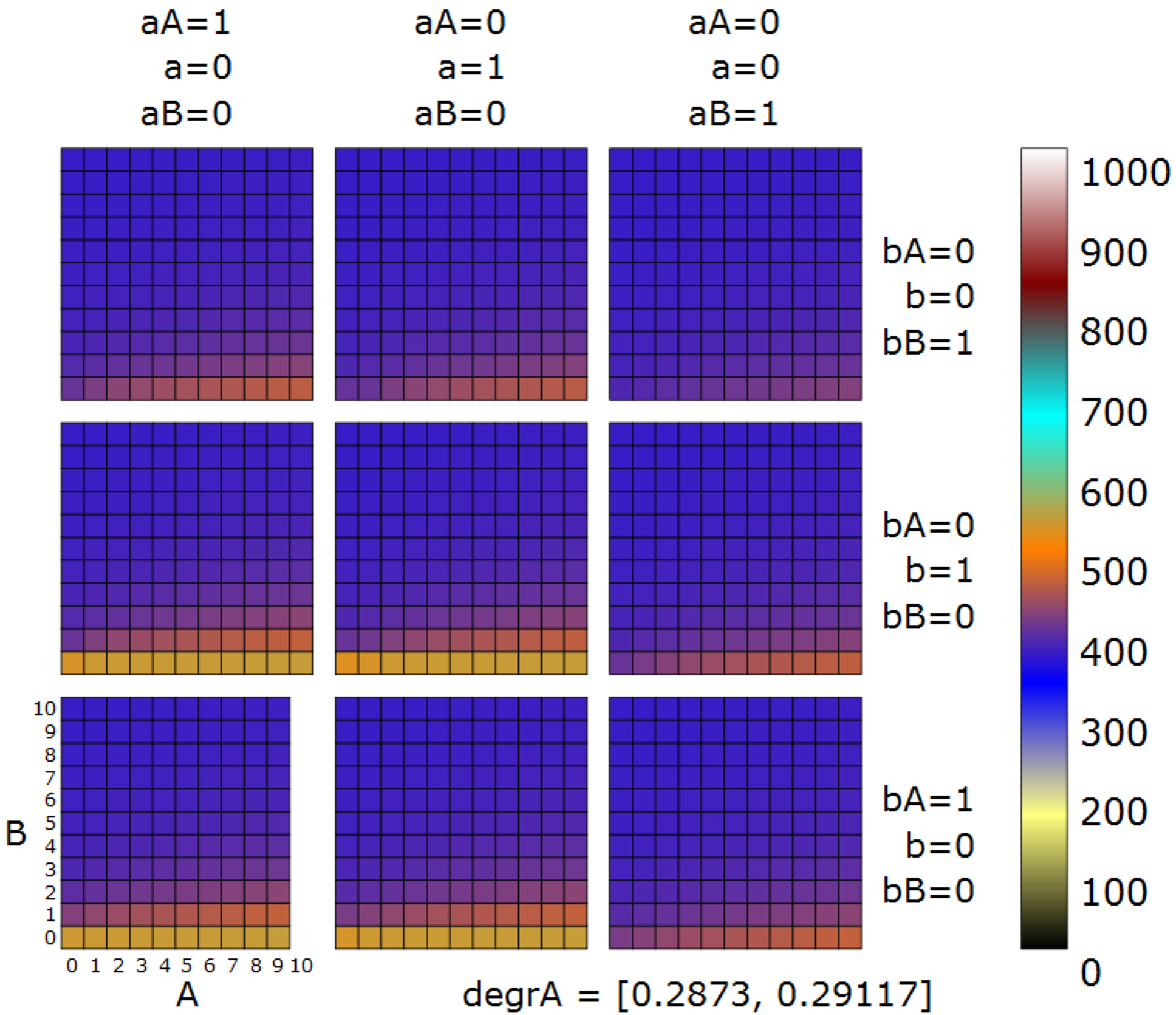
Preliminary results / 1D model, 1 parameter, 0.01 error



Preliminary results / 1D model, 1 parameter, 0.001 error



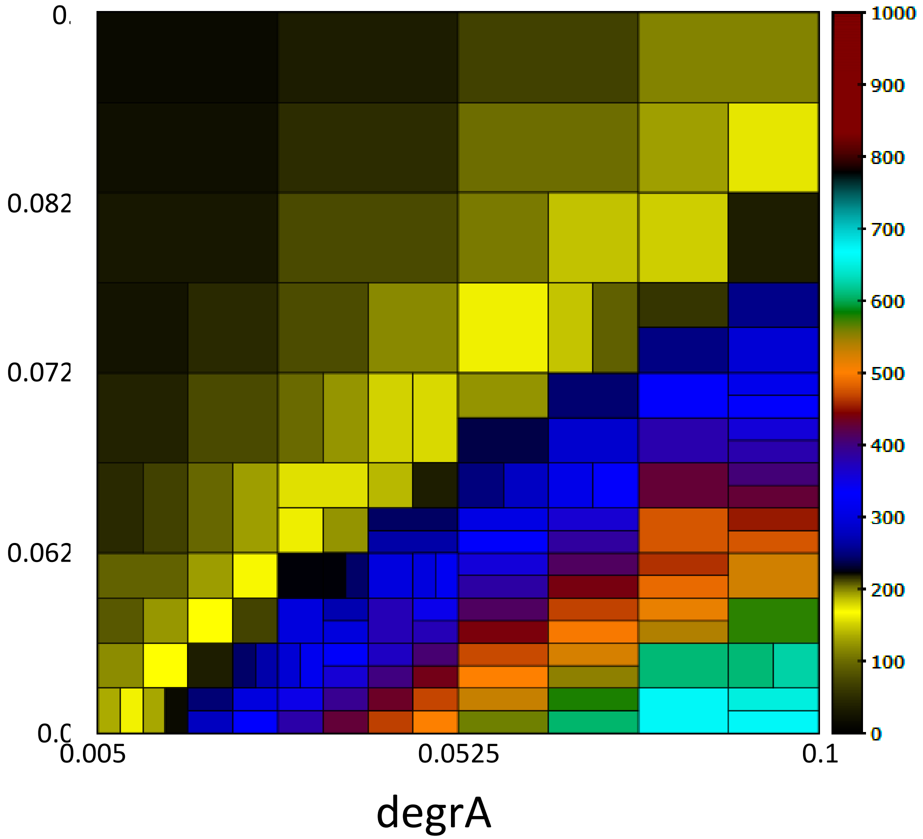
Preliminary results / State space distribution in each interval



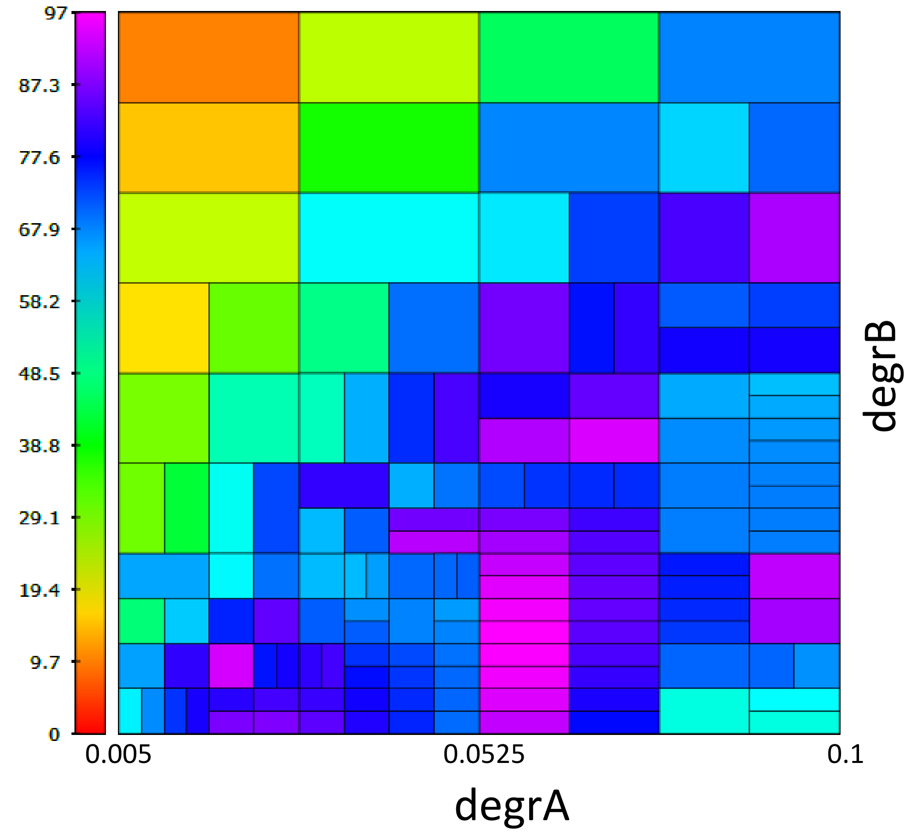
Preliminary results / 2D parameter space refinement

State #17 $\Phi :=$ R =? [C<1000] (B = 8,7,9)

Parameter space / Robustness



Parameter space / Error



Complexity

What affects the complexity?

- # of perturbed parameters and their disc/cont
- dimension of system (# of species)
- size of each dimension (# of particles of each species)
- temporal size of property formulae
- structural complexity of property formulae

Conclusion

State of Art

- Robustness = System + Property + Perturbations
- Robustness of biochemical systems is important
- Existing approaches mainly for deterministic ODEs

Aims

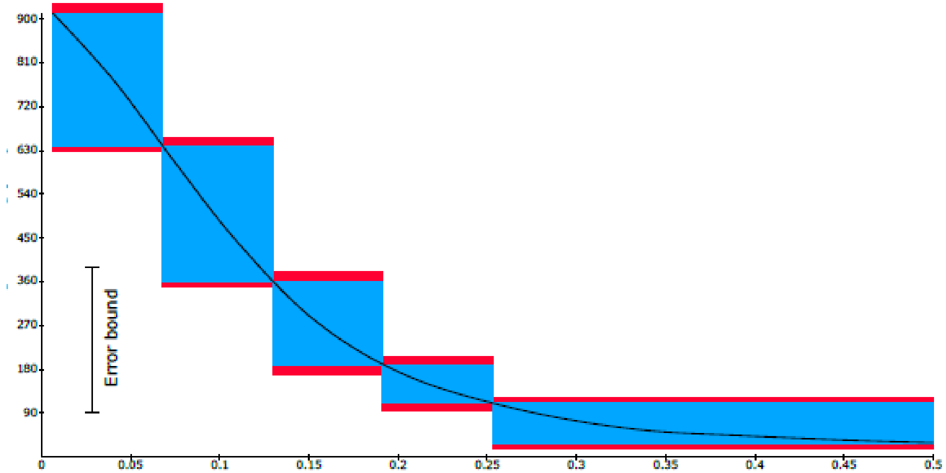
- Define robustness for stochastic systems
- Find efficient algorithms to compute robustness

How

- Exploit structure of biochemical CTMCs
- Parallelization on massively parallel platforms

$$R^{\mathcal{S}}_{\Phi,\mathbf{P}} \stackrel{def}{=} \int_{\mathbf{P}} \psi(p) D^{\mathcal{S}}_{\Phi}(p) dp$$

Thank you for your attention



Previous results

- L. Brim, J. Fabriková, S. Dražan and D. Šafránek. **Reachability in Biochemical Dynamical Systems by Quantitative Discrete Approximation**. In Proceedings of the 3rd International Workshop on Computational Models for Cell Processes (COMPMOD 2011, EPTCS, pages 97–112, 2011. *My contribution is **10%** of the whole. I implemented input parsing in the prototype algorithm and participated during discussions.*
- J. Barnat, L. Brim, I. Černá, S. Dražan, J. Fabriková, J. Láník, D. Šafránek and M. Hongwu. **BioDiVinE: A Framework for Parallel Analysis of Biological Models.** In Proceedings of 2nd International Workshop on Computational Models for Cell Processes (COMPMOD 2009), EPTCS, pages 31–45, 2009. *My contribution to the paper is **10%**. I participated in the implementation phase and evaluated the algorithm's scaling ability on a cluster.*
- J. Barnat, L. Brim, I. Černá, S. Dražan, J. Fabriková and D. Šafránek. **Computational Analysis of Large-Scale Multi-Affine ODE Models.** In International Workshop on High Performance Computational Systems Biology (HiBi 2009). IEEE Computer Society, pages 81–90, 2009. *My contribution is **15%** of the whole paper. I carried out the comparison of the different heuristics and visualized the results.*

- General definition of robustness
  - Kitano H (2007) *Towards a theory of biological robustness*. Molecular Systems Biology 3.
- CSL – Continuous Stochastic Logic
  - Aziz A, Sanwal K, Singhal V, Brayton R (1996) *Verifying continuous time Markov chains*. In: Computer Aided Verification, Springer, volume 1102 of LNCS. p. 269–276. URL http://dx.doi.org/10.1007/3-540-61474-5 75.
  - Baier C, Haverkort B, Hermanns H, Katoen J (2003) *Model-checking algorithms for continuous-time Markov chains*. IEEE Transactions on Software Engineering 29: 524–541.
- STL – Signal Temporal Logic
  - O. Maler and D. Nickovic. Monitoring temporal properties of continuous signals. In FOR-MATS/FTRTFT, p. 152–166, 2004.
  - Donzé, A., & Maler, O. (2010). Robust satisfaction of temporal logic over real-valued signals. *Formal Modeling and Analysis of Timed Systems*, p. 92–106. Springer. doi:10.1007/978-3-642-15297-9_9

Sources

- Software
  - NetLogo – http://ccl.northwestern.edu/netlogo
  - Copasi - http://www.copasi.org
  - Biocham - http://contraintes.inria.fr/BIOCHAM
  - Breach - http://www-verimag.imag.fr/~donze/breach_page.html
- Vector field visualization
  - http://kevinmehall.net/p/equationexplorer/vectorfield.html
- Wikipedia
  - http://en.wikipedia.org/wiki/Lotka_Volterra_equation
- Google Images
  - http://onlinelibrary.wiley.com/store/10.1111/j.1742-4658.2012.08719.x/asset/image_m/FEBS_8719_f1gam.gif
  - http://ars.els-cdn.com/content/image/1-s2.0-S1096717605000522-gr3.gif
  - http://wolf-happy-blog.blog.cz/profil
  - http://www.publicdomainpictures.net/view-image.php?picture=ovce-a-jeji-dite&image=124
  - http://www.nipcam.com/images/fire_ant_control_products_large.jpg
  - http://upload.wikimedia.org/wikipedia/commons/2/24/Giant_Sequoia_Sequoiadendron_giganteum_Tyler_Tree_2000px.jpg
  - http://www.surftravelcompany.com/big-wave-pics/big-wave.jpg
  - http://upload.wikimedia.org/wikipedia/commons/f/f8/Terraforming_Mars_transition_horizontal.jpg
  - http://limages.vr-zone.net/body/15884/47675_TeslaKeplerGK110_FNL_800_PR.jpg.jpeg
- Other
  - Human vs. Chimp: http://www.sciencedirect.com/science/article/pii/S0002929707640968