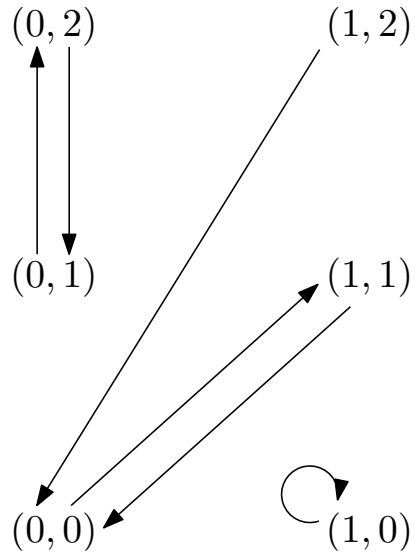
Synchronous state transition graph

- vertex set X (state space)
- edges $(x, f(x))$
  - every state has only one successor
  - attractors are fixed points and cycles corresponding to periodical points



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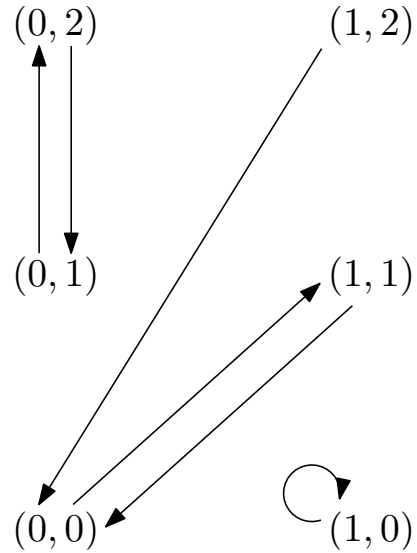
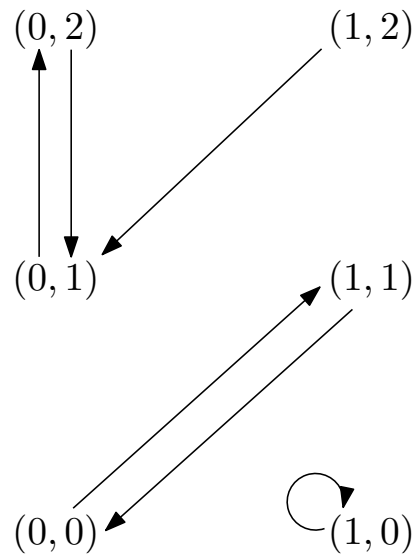


Gradual evolution

- edges (x, y) with $y_i := x_i + \mathrm{sgn}(f_i(x) - x_i)$
  - not commonly used



Sequential update

- components are updated according to a fixed sequence
- new component values are taken into account while updating

Recipe: (1) define $F^i : X \to X$ by $F^i_i(x) := f_i(x)$ and $F^i_j(x) := x_j$ for $j \neq i$

(2) choose tuple $\pi = (i_1, \ldots, i_l)$ of arbitrary length l in $\{1, \ldots, n\}^l$

(3) define $F^\pi := F^{i_l} \circ \cdots \circ F^{i_2} \circ F^{i_1}$

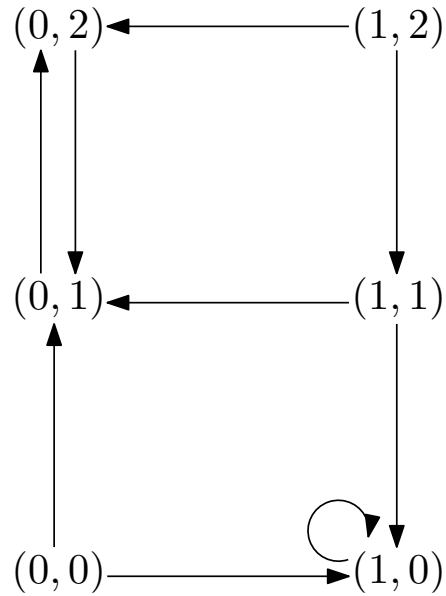
(4) analyze dynamics of F^π

- permutations of $\{1, \ldots, n\}$ often used as update order
- still very rigid constraints on trajectories

Stochastic update

choose update order randomly at each update step (probability distribution reflecting biological data)

Asynchronous update



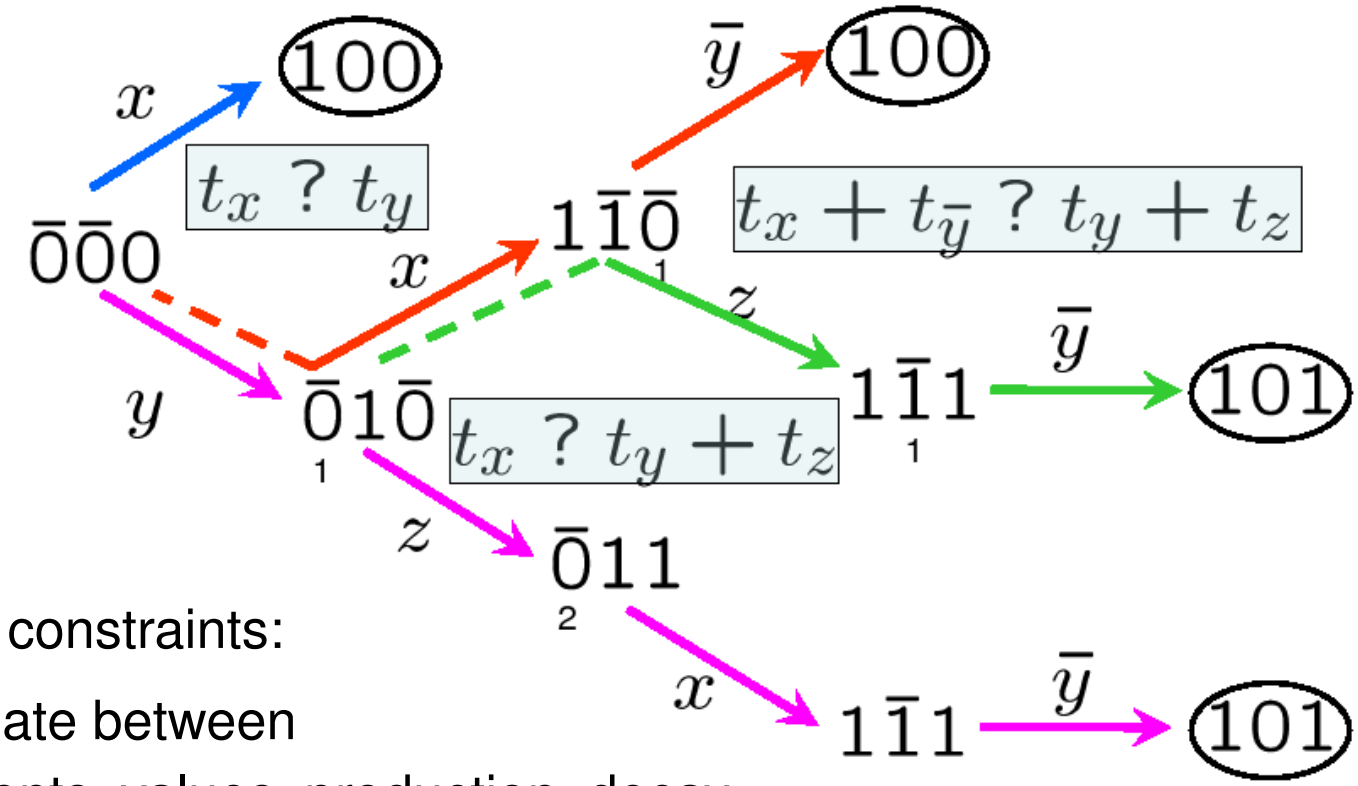
Successor (asynchronous update): x' is a successor state of x if and only if $x' = f(x) = x$ or $x'_i = x_i + \mathrm{sgn}(f_i(x) - x_i)$ for some $i \in \{1, \ldots, n\}$ satisfying $x_i \neq f_i(x)$ and $x'_j = x_j$ for all $j \neq i$.

- gradual activity level evolution
- all time delays are distinct

$\Rightarrow$ non-deterministic representation of possible behaviors

- inclusion of (partial) synchronous update possible, but not commonly used
- cyclic attractors (attr. with card. >1) may be more complex than in the deterministic case
- graph theoretical definitions for trajectories, trap sets, attractors carry over to sequential and asynchronous state transition graphs
- **synchronous and asynchronous update yield the same steady states, trajectories and cyclic attractors may differ**

Choosing your Path



Deriving time constraints:

- differentiate between components, values, production, decay
- complexity of time constraints may increase with path length (memory)
- data on process times constrain STG (modeling)
- choice of trajectories imposes time delay constraints (analysis)
  - ▷ hybrid models (PLDE systems, hybrid automata)

Stability

Analyze effects of perturbations

- change in component values (minimal perturbations)
- change in topology/update functions (structural perturbations)
- change in update order

on dynamical aspects

- behavior originating in some initial state (states visited, reachable attractors, number of transients)
- attractors and basins of attraction

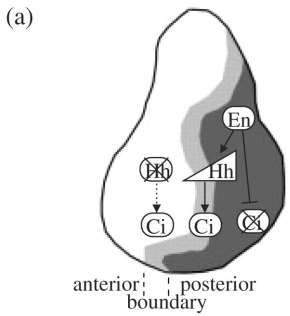
Derrida plot: study development of small fluctuations via evolution of Hamming distance over time

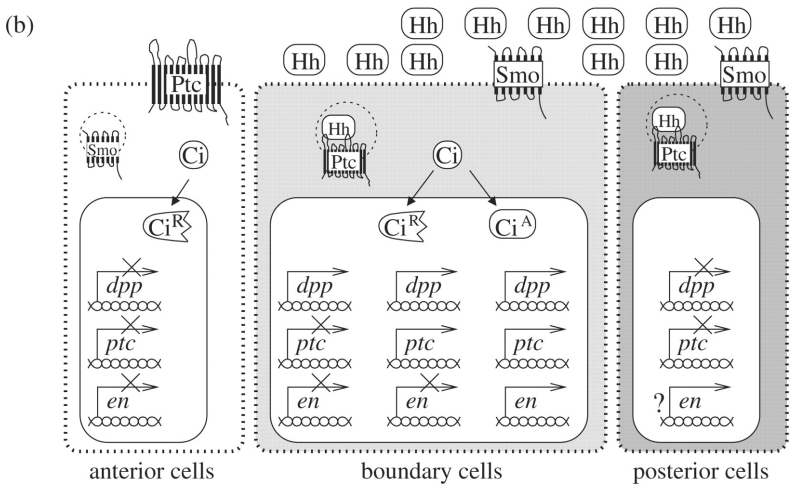
Update issues: compare behavior under different update assumptions

Patterning of the *Drosophila* wing disc

A. González, C. Chaouiya, D. Thieffry, *Logical modelling of the role of the Hh pathway in the patterning of the Drosophila wing disc*, Bioinformatics 24, 2008

Aim: qualitative model of anterior-posterior boundary definition during wing disc development





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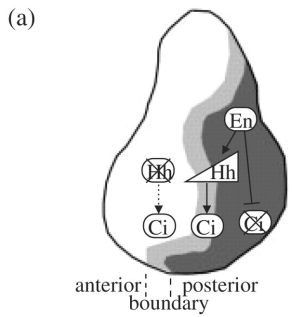
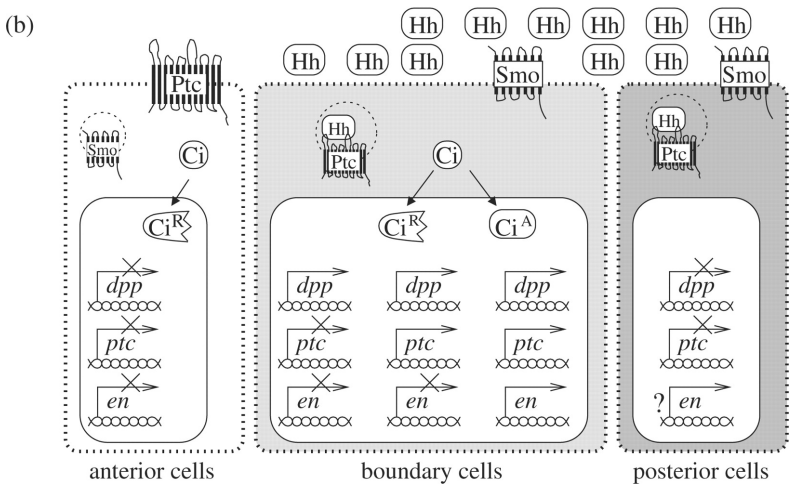




Consistent discrete representation of

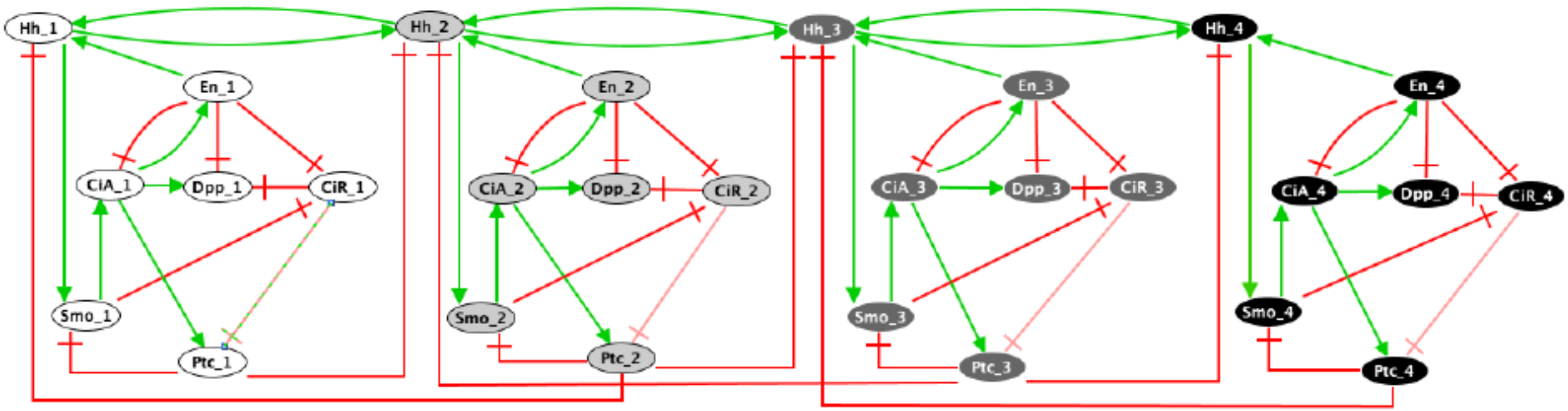
- gene regulation
- signal transduction
- diffusion
- sequestration

as intercellular process

Modeling

intercellular process:	four virtual cells represent anterior (c1), boundary (c2, c3) and posterior compartments (c4)
regulation:	positive/negative interactions
signal transduction:	path of interactions
diffusion:	symmetrical positive interactions between adjacent Hh nodes
sequestration:	negative edge from Ptc to Hh nodes of adjacent cells

+ multi-value + logical function



Simplifications

- several components omitted in signal transduction, emission, reception
- signal transduction mechanism (Smo under direct control of Hh and Ptc)
- omission of further target genes depending on concentration gradient
- ignoring spatial information concerning single cells (membrane, interior, exterior)
- model cells represent regions of AP boundary

The model

Regulatory node	Incoming interactions	Experimental data	Logical function
CiA_i	$Smo_i \rightarrow CiA_i$	Clones for *smo*$^-$ in the boundary result in loss of CiA targets such as En, Ptc and Dpp (Chen and Struhl, 1996; Strigini and Cohen, 1997). By contrast, overexpression of Smo results in the accumulation of full-length Ci in anterior cells (Jia *et al.*, 2003).	CiA_i=1 IF NOT($En_i^{[2]}$) AND $Smo_i^{[1]}$ CiA_i=2 IF NOT($En_i^{[2]}$) AND $Smo_i^{[2]}$
	$En_i \dashv CiA_i$	Loss of En function upregulates *ci* expression in posterior cells, whereas ectopic En activity represses *ci* expression in anterior cells (Dominguez *et al.*, 1996; Eaton and Kornberg, 1990).	
CiR_i	$Smo_i \dashv CiR_i$ $En_i \dashv CiR_i$	See evidence of CiA regulation by En and Smo.	CiR_i=1 IF NOT($En_i^{[2]}$) AND NOT($Smo_i^{[1,2]}$)
Dpp_i	$CiA_i \rightarrow Dpp_i$	Expression of a *ci* allele that cannot be proteolyzed induces high levels of *dpp* expression anteriorly (Méthot and Basler, 1999).	Dpp_i=2 IF ($CiA_i^{[1,2]}$ AND NOT($En_i^{[1,2]}$) Dpp_i=1 IF ($CiA_i^{[1,2]}$ AND $En_i^{[1,2]}$) OR (NOT($CiA_i^{[1,2]}$ AND NOT($En_i^{[1,2]}$) AND NOT($CiR_i^{[1]}$))
	$CiR_i \dashv Dpp_i$	Cells mutant for *ci*$^-$ in anterior and boundary cells express low levels of *dpp* (Méthot and Basler, 1999).	
	$En_i \dashv Dpp_i$	Loss of En function in posterior cells induces *dpp* expression (Méthot and Basler, 1999; Sanicola *et al.*, 1995; Zecca *et al.*, 1995), whereas ectopic En in boundary cells downregulates *dpp* expression (de Celis and Ruiz-Gómez, 1995; Sanicola *et al.*, 1995).	
En_i	$CiA_i \rightarrow En_i$	In the absence of PKA, CiA is upregulated and induces *en* expression (Wang *et al.*, 1999), whereas in *ci*$^-$ mutant cells in the boundary, CiA is lost and downregulates *en*. By contrast, posterior *en* expression is not affected by the *ci*$^-$ mutation (Aza-Blanc *et al.*, 1997; Méthot and Basler, 1999; Strigini and Cohen, 1997).	En_i=1 ($i \neq 4$) IF $CiA_i^{[2]}$ En_4=2
Hh_i	$Hh_j \rightarrow Hh_i$	Loss of Hh in posterior cells reduces Hh signalling non cell-autonomously in boundary cells (Basler and Struhl, 1994), whereas ectopic *hh* expressing cells in the anterior compartment non cell-autonomously upregulate the Hh pathway (Zecca *et al.*, 1995).	Hh_i=2 IF $En_i^{[2]}$ OR ($Hh_j^{[2]}$ AND $Hh_k^{[2]}$) OR ($Hh_j^{[2]}$ AND NOT($Ptc_j^{[2]}$)) OR ($Hh_j^{[1]}$ AND NOT($Ptc_j^{[2]}$) AND $Hh_k^{[1]}$ AND NOT($Ptc_k^{[2]}$)) OR ($Hh_j^{[2]}$ AND $Ptc_j^{[2]}$ AND $Hh_k^{[1]}$ AND NOT($Ptc_k^{[2]}$))
	$Ptc_j \dashv Hh_i$	In the *ptc*$^-$ discs, the stripe of the reporter *ptc-lacZ* is broader (Chen and Struhl, 1996).	Hh_i=1 IF NOT(En_i^2) AND (($Hh_j^{[1]}$ AND NOT($Ptc_j^{[2]}$) AND NOT($Hh_k^{[1,2]}$)) OR ($Hh_j^{[2]}$ AND $Ptc_j^{[2]}$ AND NOT($Hh_k^{[1,2]}$)) OR ($Hh_j^{[1]}$ AND $Ptc_j^{[2]}$ AND $Hh_k^{[2]}$ AND $Ptc_k^{[2]}$)
	$En_i \rightarrow Hh_i$	In posterior *en*$^-$ mutant cells, *hh* is downregulated (Alexandre and Vincent,	

Results

Table 2. Stable states reached for the wild-type situation (vector 1) and for genetic alterations (vectors 2-12)

Gene	CiA				CiR				Dpp				Ptc				Smo				Hh				En			
Cell	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1 WT	0	1	2	0	1	0	0	0	0	2	1	0	1	2	2	1	0	1	2	2	0	1	2	2	0	0	1	2
2 posterior hh^-	0	**0**	**0**	0	1	**1**	**1**	0	**0**	**0**	**0**	0	1	**1**	**1**	1	0	**0**	**0**	**0**	0	**0**	**0**	⓪	0	0	**0**	2
3 boundary ptc^-	**2**	**2**	2	0	**0**	0	0	0	**1**	**1**	1	0	**2**	⓪	⓪	1	**2**	**2**	2	2	**2**	**2**	2	2	**1**	**1**	1	2
4 boundary $Smo-$	**2**	**0**	**0**	0	**0**	**1**	**1**	0	**1**	**0**	**0**	0	**2**	**1**	**1**	1	**2**	⓪	⓪	2	**2**	**2**	2	2	**1**	**0**	0	2
5 anterior Smo^+	**1**	1	2	0	**0**	0	0	0	**2**	2	1	0	**2**	2	2	1	①	1	2	2	0	1	2	2	0	0	1	2
6 anterior ci^-	⓪	1	2	0	⓪	0	0	0	**1**	2	1	0	1	2	2	1	0	1	2	2	0	1	2	2	0	0	1	2
	⓪	**2**	2	0	⓪	0	0	0	**1**	**1**	1	0	1	2	2	1	**2**	**2**	2	2	**1**	**2**	2	2	0	**1**	1	2
7 boundary ci^-	**2**	⓪	⓪	0	**0**	⓪	⓪	0	**1**	**1**	1	0	**2**	**1**	**1**	1	**2**	**2**	2	2	**2**	**2**	2	2	**1**	0	**0**	2
8 cir^+ disc	**2**	**2**	2	0	②	②	②	②	**1**	**1**	1	0	1	**1**	**1**	0	**2**	**2**	2	2	**2**	**2**	2	2	**1**	**1**	1	2
9 half boundary CiA^-	⓪	⓪	2	0	**0**	0	0	0	**1**	**1**	1	0	1	**1**	2	1	**2**	**2**	2	2	**2**	**2**	2	2	0	0	1	2
10 half boundary CiA^+	②	②	2	0	1	0	0	0	**1**	**1**	1	0	2	2	2	1	0	1	2	2	0	1	2	2	**1**	**1**	1	2
11 boundary high *en*	**2**	**0**	**0**	0	**0**	0	0	0	**1**	**0**	**0**	0	**2**	**1**	**1**	1	**2**	**2**	2	2	**2**	**2**	2	2	**1**	②	②	2
12 posterior hypomorph *en*	0	**0**	**0**	0	1	**1**	**1**	**1**	0	**0**	**0**	0	1	**1**	**1**	1	0	**0**	**0**	**0**	0	**0**	**0**	**0**	0	0	**0**	①

- simulation of wild type $\longrightarrow$ unique stable state capturing AP boundary patterning
- simulation of various mutants by fixing levels of misexpressed genes, results in agreement with experimental observations
  data used for modeling?
- predictions (not yet experimentally verified)

Kauffman networks

Question by S. Kauffman: How did order evolve in organisms?

- selection
- intrinsic properties of networks

Cell differentiation (S. Kauffman, 1969)

- structure of gene regulatory networks unknown
- regulatory rules unknown

but

- GRNs can be modeled as Boolean networks
- check for dynamical properties of biological importance in random networks

Properties of interest

Aspects of order

- small attractors
- big basins of attraction, small number of attractors
- short transients (steps leading from an initial state to an attractor)
- low sensitivity to perturbations

Biological systems

- order and complexity
- robustness and adaptability

Random *NK* Boolean networks

Construct (big) random networks with

- N vertices
- K predecessors for each vertex
- update function based on interaction graph

$\longrightarrow$ network ensembles

Procedure

- choose randomly inputs for vertices
- randomly assign update function per vertex

random interaction graph and update logic
$\Rightarrow$ **strongly disordered system**

Can orderly behavior emerge?