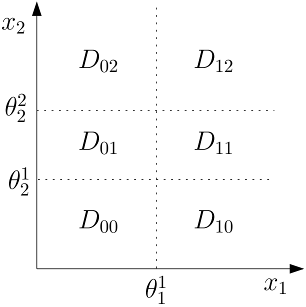
From PLDE to FDS



- regular domain D_s is identified with qualitative state $s = (s_1, \ldots, s_n)$, integer values describe position w.r.t. thresholds
- trajectories tend towards target value $\Phi(D)$
- target value position in a regular domain can be described by corresponding state $s^{\Phi(D)}$

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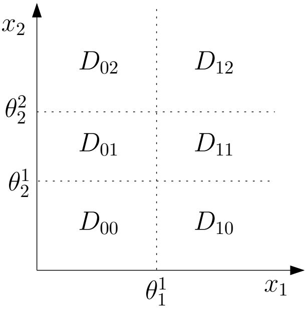

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Describe the system dynamics by a function

$$f : \{s \mid D_s \text{ regular domain}\} \to \{s \mid D_s \text{ regular domain}\},\ s \mapsto s^{\Phi(D)}$$

Consider “trajectories” $(s, f(s), f(f(s)), ...)$

Discrete modeling

- system description by means of discrete functions
  - including structural information: network components and dependencies
  - capturing of interaction character and impact

  → predicting/analyzing dynamics

Hypothesis: kinetic details of interactions less important than network organization

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Ingredients

- system with n components α_i interpreted as variables in $X_i := \{0, \ldots, p_i\}$ with $p_i \in \mathbb{N}$
- state space $X := X_1 \times \cdots \times X_n$
- n functions $f_i : X \to X_i$ capture rules to calculate future value of α_i from current value of its regulators
- system description: discrete function $f = (f_1, \ldots, f_n) : X \to X$

  E.g. Boolean networks: $p_i = 1$ for all $i \in \{1, \ldots, n\}$

Dynamics

Consider $f : X \to X$, $X = \prod_{i=1}^{n} X_i$, $X_i = \{0, 1, \dots, p_i\}$, $p_i \in \mathbb{N}$, (FDS)

and dynamics $(f^k(x))_{k \in \mathbb{N}},\ x \in M,$ with $f^1 = f,\ f^k = f \circ f^{k-1}$

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State transition graph $S(f)$ of f

- vertex set X (state space, exponential in n)
- edge set $\{(x, f(x)) \mid x \in X\}$ – **synchronous update**
- trajectories: infinite paths $(x, f(x), f^2(x), \ldots)$ in $S(f)$

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Note conceptual differences to ODE/PLDE description:

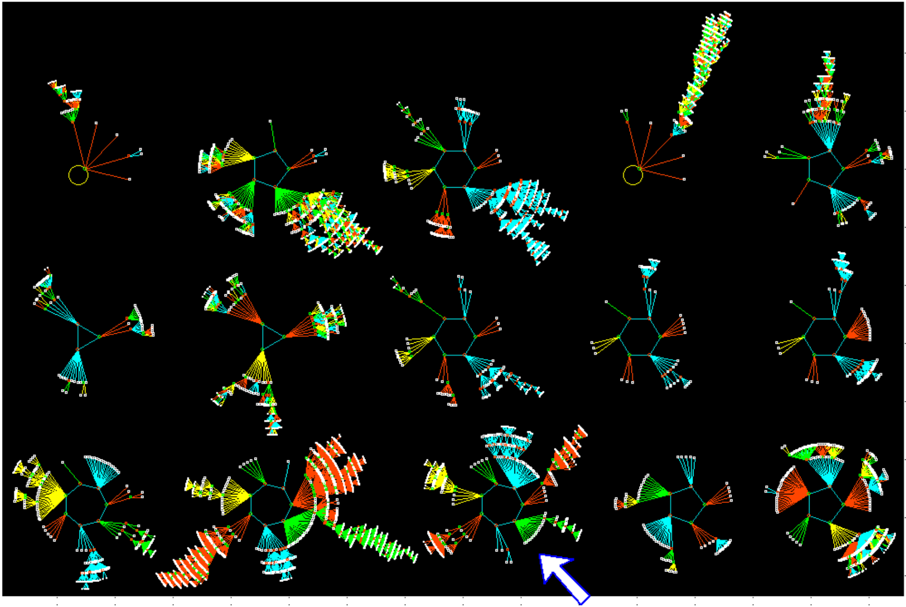
explicit description of trajectories, trajectories can merge

Consequences of synchronous update and finite state space

- each trajectory “ends” in a cycle

→ attractor: terminal strongly connected components of $S(f)$

Finite dynamics (n=13)



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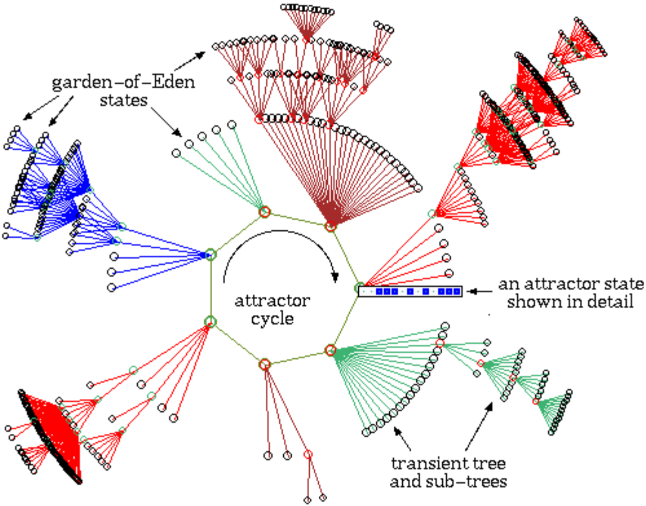
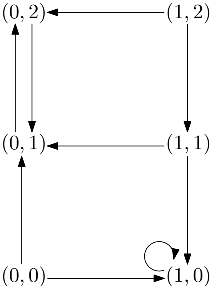

garden-of-Eden states
an attractor state shown in detail
attractor cycle
transient tree and sub-trees

Asynchronous update



State transition graph

- vertex set X
- edges $x \to x'$ iff $x' = f(x) = x$ 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 $j \neq i$ **(asynchronous update)**
  - gradual activity level evolution
  - all time delays are distinct

  $\rightarrow$ **more realistic for modeling e.g. biological systems**

  $\Rightarrow$ non-deterministic representation of possible behaviors
- attractors and trajectories may differ from the synchronous case

asynchronous dynamics is more complex and harder to analyze

Structure

Given $f : X \to X$, $X = \prod_{i=1}^{n} X_i$, $X_i = \{0, 1, \dots, p_i\}$, $p_i \in \mathbb{N}$ (FDS)

Interaction graph $G(f)$

- vertices represent network components
- directed edges capture interactions, may be labeled
  - signs carry information on interaction character
  - thresholds specify conditions on edge activity

  → labeled interaction graphs may be multigraphs (parallel edges)

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Deriving $G(f)$ from f

- $\alpha_j \to \alpha_k$ iff f_k depends on the variable x_j, i.e., there exists $x \in X$ with $f_k(x) \neq f_k(\tilde{x})$ where $\tilde{x}_j \neq x_j$ and $\tilde{x}_l = x_l$ for all $l \neq j$
- signs and labels can also be derived mathematically from f

$\Rightarrow$ $G(f)$ represents functional network topology of f

Modeling

Modeling specific systems often starts with structural information:

- translate data on regulatory processes into directed, possibly labeled (multi)graphs

Definition An *interaction (multi-)graph* I is a finite (labeled) directed (multi)graph. (Vertices are understood as variables.)

vertex: component (genes, proteins, chemical complexes,...), set of components (similar function, identification {gene, RNA, protein},...), signal,...

edge: inhibiting/activating activity (TFs, enzymes,...), complex forming, information flow,...

value: activity status, concentration, configuration,...

- translate behavioral rules into discrete function $f : X \to X$
  - for each component decide the impact of its predecessors in a given state on its value $\to$ choice of parameters

Consistency: $I = G(f)$

Exploring the Structure

Consider interaction graph $I = (V, E)$

Use graph theoretical characteristics and measures

- quantify organizational features of I
    - importance of nodes
    - reachability among nodes
    - homogeneity/heterogeinity w.r.t. a given property
- relate to biological features
    - robustness, sensitivity, control,...
    - identify modules with characteristic function

Degree distribution and clustering

- **degree** of a node: # of edges originating (**outdegree**) or ending (**indegree**) in the node
- **hubs:** highest degree nodes
- **degree distribution** $P(k)$: fraction of nodes with degree k (indegree/outdegree distribution)
  [cellular networks are often scale-free]
- **neighborhood** of a node v: set of nodes $\neq v$ adjacent to v (in/out-neighborhood)
- **clique**: completely connected subgraph
- **clustering coefficient** of a node: ratio of # of edges in neighborhood and # of edges if neighborhood were a clique
  [large average clustering coefficients indicate redundancy, cohesiveness; observed in protein-protein interaction and metabolic networks]

Paths and connectivity

- **distance** between two nodes: shortest path length connecting the nodes
- **small world**: average shortest path length of large networks stays small [facilitates rapid spread of information in response to input; signal transduction, protein interaction, metabolic networks]
- **path redundancy** [robustness]
- **betweenness centrality** of node *v*: ratio of # shortest paths from *s* to *t* through *v* and total # of shortest *st*-paths
  [importance of a node in flow from sources to sinks]
- **connectivity** of the network: existence of paths between every pair of nodes (distinguish directed/undirected graphs)
  - **strongly connected** directed graphs: all node pairs connected in both directions
  - **strongly connected components:** maximal subgraphs that are strongly connected $\rightarrow$ acyclic scc-graph with initial and terminal components
    [modularity of signaling networks]