LCCC Workshop
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Pattern Formation in Multi-Cellular Systems

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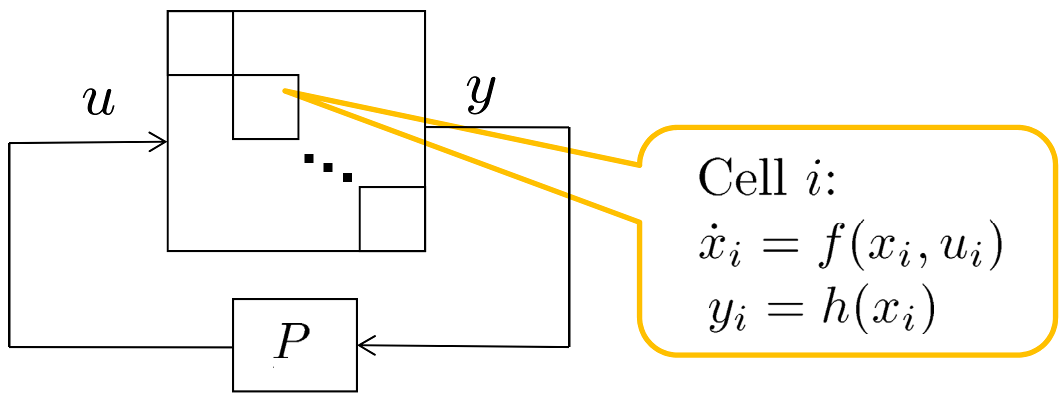
How do spatial gene expression patterns form?

- Fundamental problem in developmental biology
- New challenge for synthetic biology
- Mathematical analysis and design hampered by large-scale models

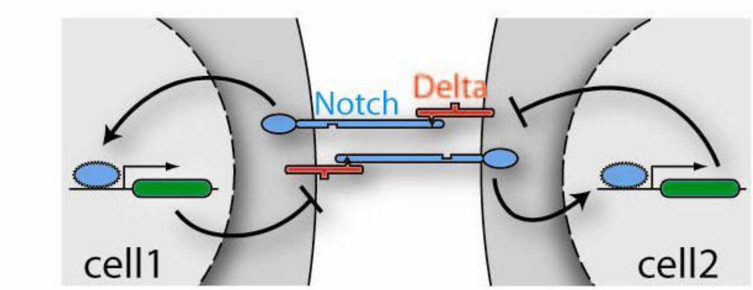
Decompositional Approach: Exploit I/O properties of subsystems (cells) and their coupling structure (diffusion[1], contact signaling, etc.)



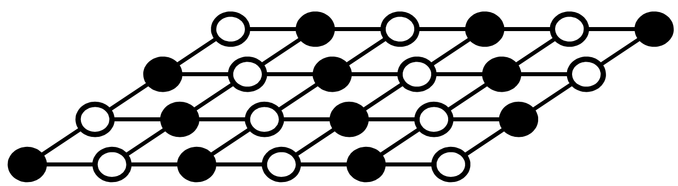
[1] Hsia, Holtz, Huang, Maharbiz, Arcak, "A feedback quenched oscillator produces Turing patterning with one diffuser." PLoS Computational Biology, 2012.

Contact-Mediated Inhibition

Common patterning mechanism in multi-cellular organisms, *e.g.*, Notch signaling in mammalian cells:



Delta in one cell inhibits production of Delta in adjacent cells:



Literature: Simulations for specific models[2,3,4] of Notch signaling. Patterning analysis under restrictive assumptions (*e.g.*, two cells).

This talk: A scalable technique for predicting patterns, applicable to a broad class of systems.

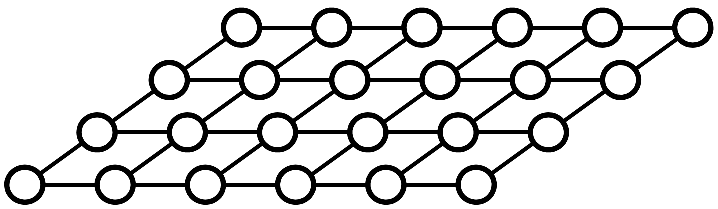
[2] Collier *et al. J.Theo.Bio.* 1996; [3] Ghosh & Tomlin *IEE Sys.Bio*. 2004; [4] Sprinzak *et al. PLoS Comp.Bio. 2011*

Interconnected Dynamical Model

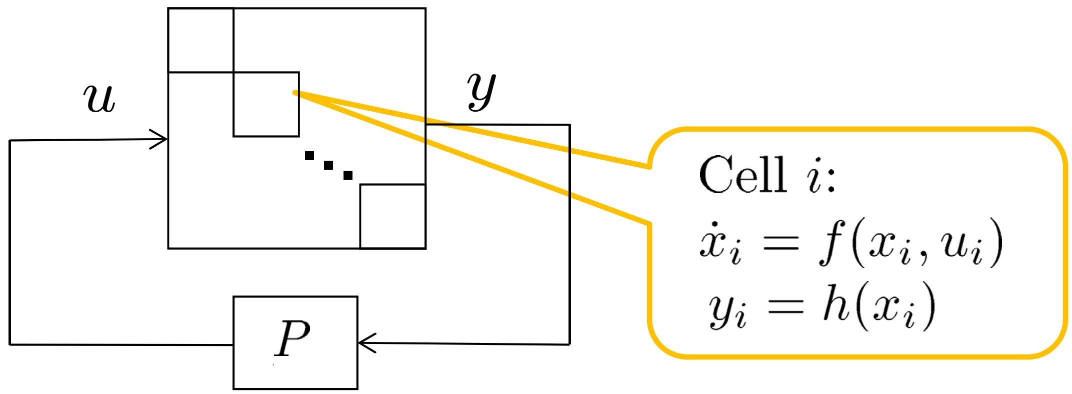
Define scaled adjacency matrix for the contact graph:

$$p_{ij} = \begin{cases} {d_i}^{-1} & \text{if vertices } i \text{ and } j \text{ are adjacent} \\ 0 & \text{otherwise} \end{cases}$$

where d_i : vertex degree. Eigenvalues of P: $-1 \leq \lambda_N \leq \cdots \leq \lambda_1 = 1$

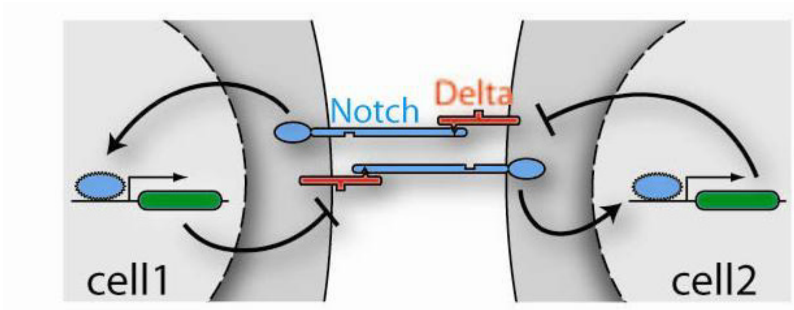


Reaction network:



$u_i = \langle y_j \rangle_i$ (average y_j over neighbors j of cell i)

Example:



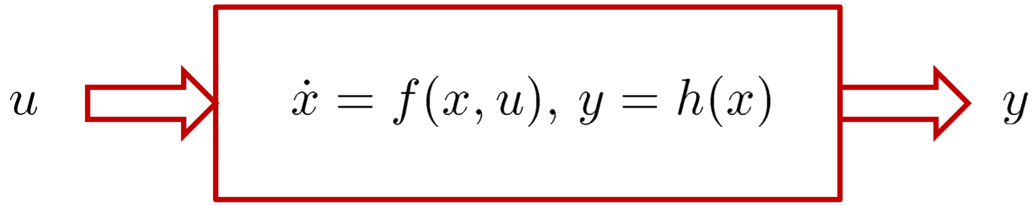
$$\begin{aligned}\dot{N}_i &= \beta - \gamma N_i - kN_i\langle D_j\rangle_i \\ \dot{D}_i &= g(S_i) - \gamma D_i - kD_i\langle N_j\rangle_i \\ \dot{S}_i &= -\gamma S_i + kN_i\langle D_j\rangle_i.\end{aligned}$$

Define input and output: $u_i = \begin{bmatrix} \langle N_j\rangle_i \\ \langle D_j\rangle_i \end{bmatrix} \quad y_i = \begin{bmatrix} N_i \\ D_i \end{bmatrix}$

I/O model for each cell:

$$u = \begin{bmatrix} u_{(1)} \\ u_{(2)} \end{bmatrix} \Rightarrow \boxed{\begin{aligned}\dot{N} &= \beta - \gamma N - kNu_{(2)} \\ \dot{D} &= g(S) - \gamma D - kDu_{(1)} \\ \dot{S} &= -\gamma S + kNu_{(2)}\end{aligned}} \Rightarrow y = \begin{bmatrix} N \\ D \end{bmatrix}$$

Assumptions on the I/O Model



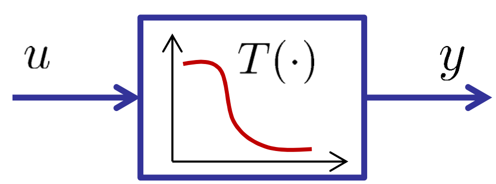
1) For each constant u there is a hyperbolic, globally asymptotically stable steady-state: $x = S(u)$.

2) The steady-state I/O map:

$$T(u) := h(S(u))$$

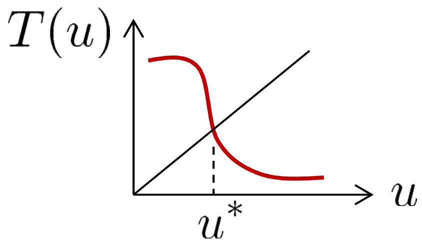
is decreasing: $u \succeq v \;\Rightarrow\; T(u) \preceq T(v)$.

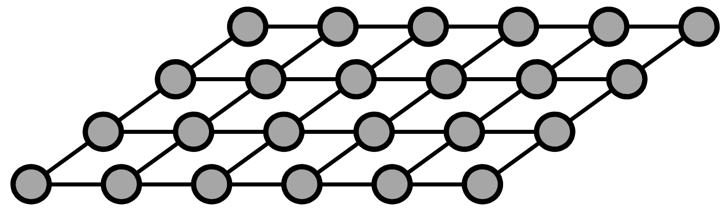
3) For simplicity, henceforth assume SISO, differentiable $T(\cdot)$, *and* $T'(u) < 0$ *for all* u



The Homogeneous Steady-State

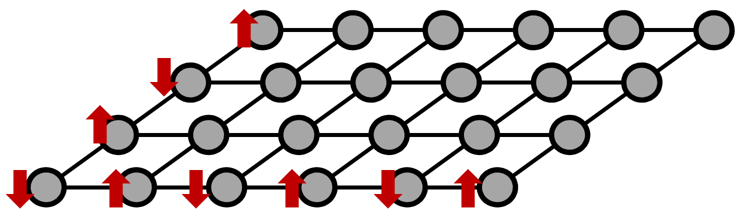
Fixed point of $T(\cdot)$ determines a spatially homogeneous steady-state:

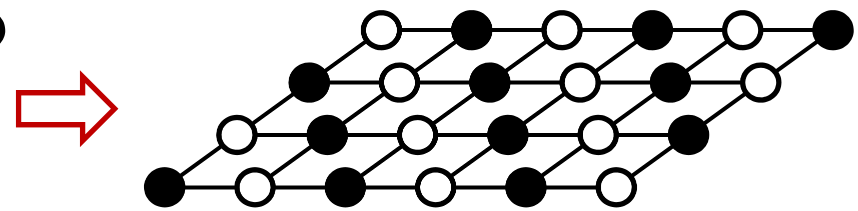




$$u^* = T(u^*) \qquad x^i = S(u^*),\ i = 1, \cdots, N$$

and instability of this steady-state sets the stage for patterning:





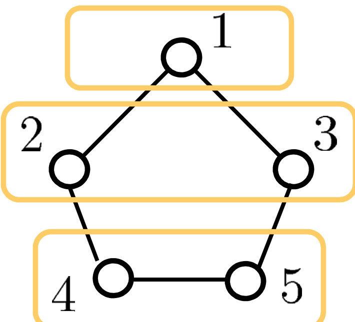
Instability Criterion: $\lambda_N < 0$ and $|T'(\mathbf{u}^*)| > |\lambda_N|^{-1}$

where λ_N is the smallest eigenvalue of P.

Pattern Templates from Graph Partitioning

A **partition** of the vertex set into classes $O_1, \cdots, O_r$ is **equitable** if $\exists\ \overline{p}_{ij},\ i,j = 1,\ldots,r$, such that the adjacency matrix P satisfies:

$$\sum_{l \in C_j} p_{kl} = \overline{p}_{ij} \quad \forall k \in O_i$$



$$P = \left[\begin{array}{c|cc|cc} 0 & 1/2 & 1/2 & 0 & 0 \\ \hline 1/2 & 0 & 0 & 1/2 & 0 \\ 1/2 & 0 & 0 & 0 & 1/2 \\ \hline 0 & 1/2 & 0 & 0 & 1/2 \\ 0 & 0 & 1/2 & 1/2 & 0 \end{array}\right] \qquad \overline{P} = \begin{bmatrix} 0 & 1 & 0 \\ 1/2 & 0 & 1/2 \\ 0 & 1/2 & 1/2 \end{bmatrix}$$

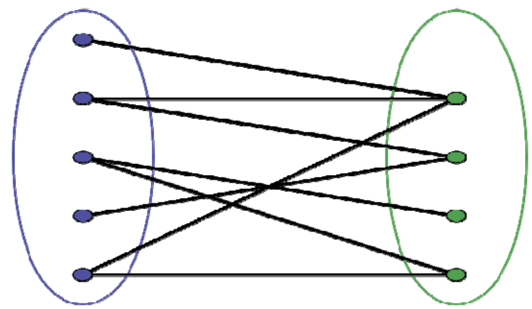
Look for steady-states where vertices in the same class are identical:

$$\begin{bmatrix} u_1 \\ \vdots \\ \vdots \\ u_N \end{bmatrix} = P \begin{bmatrix} T(u_1) \\ \vdots \\ \vdots \\ T(u_N) \end{bmatrix} \quad \xRightarrow[\forall i \in O_j]{u_i = w_j} \quad \begin{bmatrix} w_1 \\ \vdots \\ w_r \end{bmatrix} = \overline{P} \begin{bmatrix} T(w_1) \\ \vdots \\ T(w_r) \end{bmatrix}$$

(reduced)

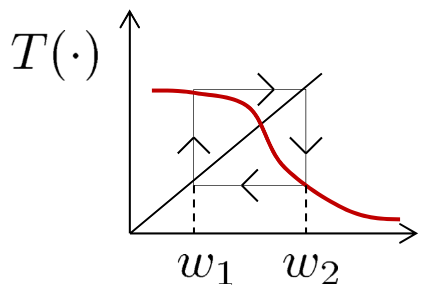
Example: Bipartite Graphs

$$P = \left[\begin{array}{c|c} 0 & P_{12} \\ \hline P_{21} & 0 \end{array}\right] \Rightarrow \overline{P} = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$$

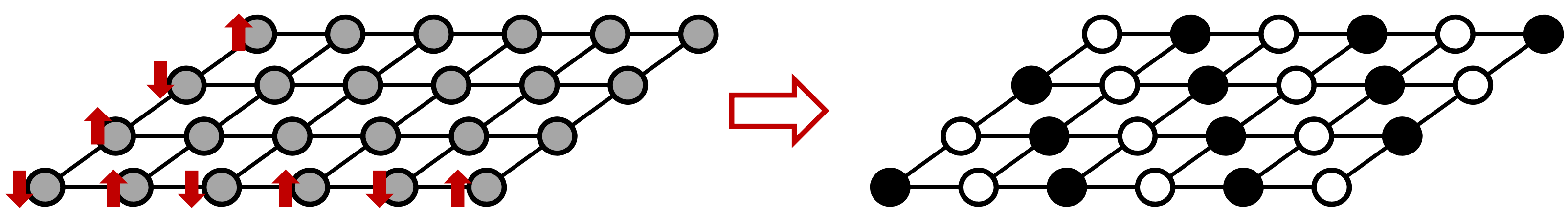


Steady-states consistent with the bipartition are period-two solutions of the I/O map:

$$\begin{bmatrix} w_1 \\ w_2 \end{bmatrix} = \overline{P} \begin{bmatrix} T(w_1) \\ T(w_2) \end{bmatrix}$$



A period-two solution indeed exists if $|T'(u^*)| > 1$ at the fixed pt. u^*:



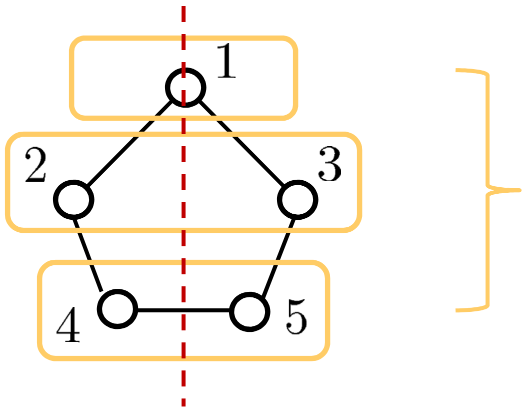
Equitable Partitions from Symmetries

Given graph $\mathcal{G}(V, E)$, an **automorphism** is a permutation $g : V \to V$ such that if $(i, j) \in E$ then also $(gi, gj) \in E$.

The **automorphism group**, $Aut(\mathcal{G})$, is the set of all automorphisms.

$H \subset Aut(\mathcal{G})$ is a **subgroup** if it is closed under composition & inverse.

The action of all permutations in subgroup H forms an equitable partition of the vertex set into **orbits**, $O_i = \{hi : h \in H\}$.



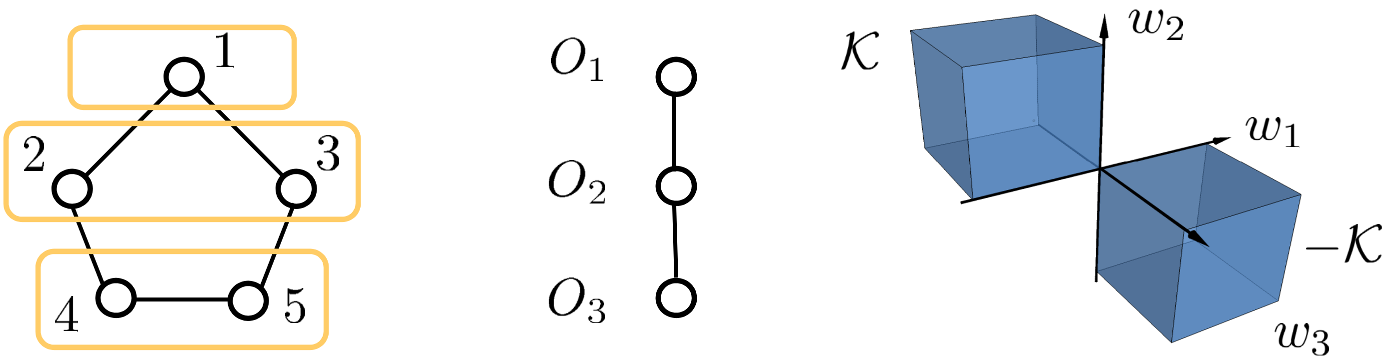
orbits generated by subgroup:
$H = \{Id, 13254\}$

Computational discrete algebra software, *e.g.* GAP, identify subgroups

Which Partitions Admit Patterns?

Given a partition, define *reduced graph* $\overline{G}$ with vertex and edge sets:

$$\overline{V} = \{O_1, \ldots, O_r\} \quad \overline{E} = \{(O_i, O_j) : i \neq j, \overline{p}_{ij} \neq 0 \text{ or } \overline{p}_{ji} \neq 0\}$$



Theorem: Suppose $\overline{G}$ is bipartite and define the cone:

$$\mathcal{K} = \{w \in \mathbb{R}^r : \ w_i w_j \leq 0 \text{ if } i \text{ and } j \text{ are adjacent in } \overline{G}\}.$$

If for every eigenvector of $\overline{P}$ in $\mathcal{K} \cup -\mathcal{K}$:

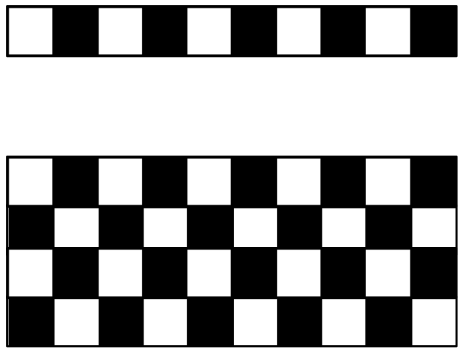
$$\lambda < 0 \quad \text{and} \quad |T'(u^*)| > |\lambda|^{-1}$$

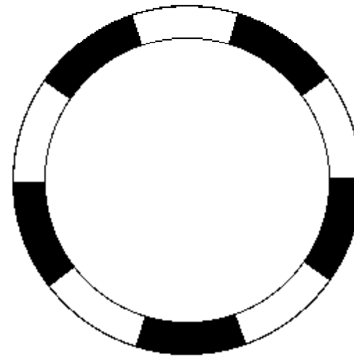
then **(reduced)** admits a nonhomogeneous solution.

Examples

Bipartite Graphs:

Checkerboard patterns emerge when $|T'(u^*)| > 1$:

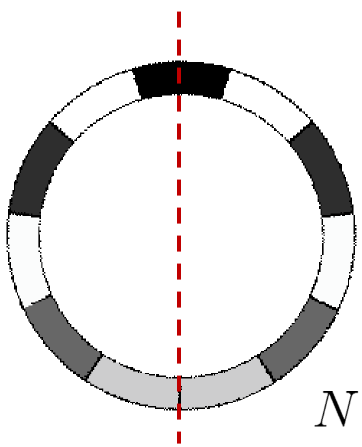




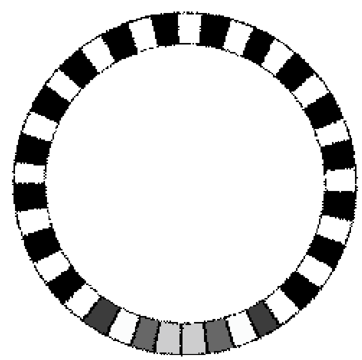
even N

Odd-Length Cycles:

A symmetric pattern emerges when $|T'(u^*)| > \sec(\pi/N)$:

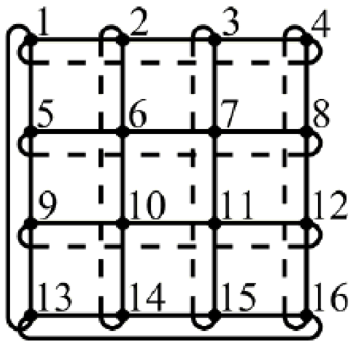


$N = 11$



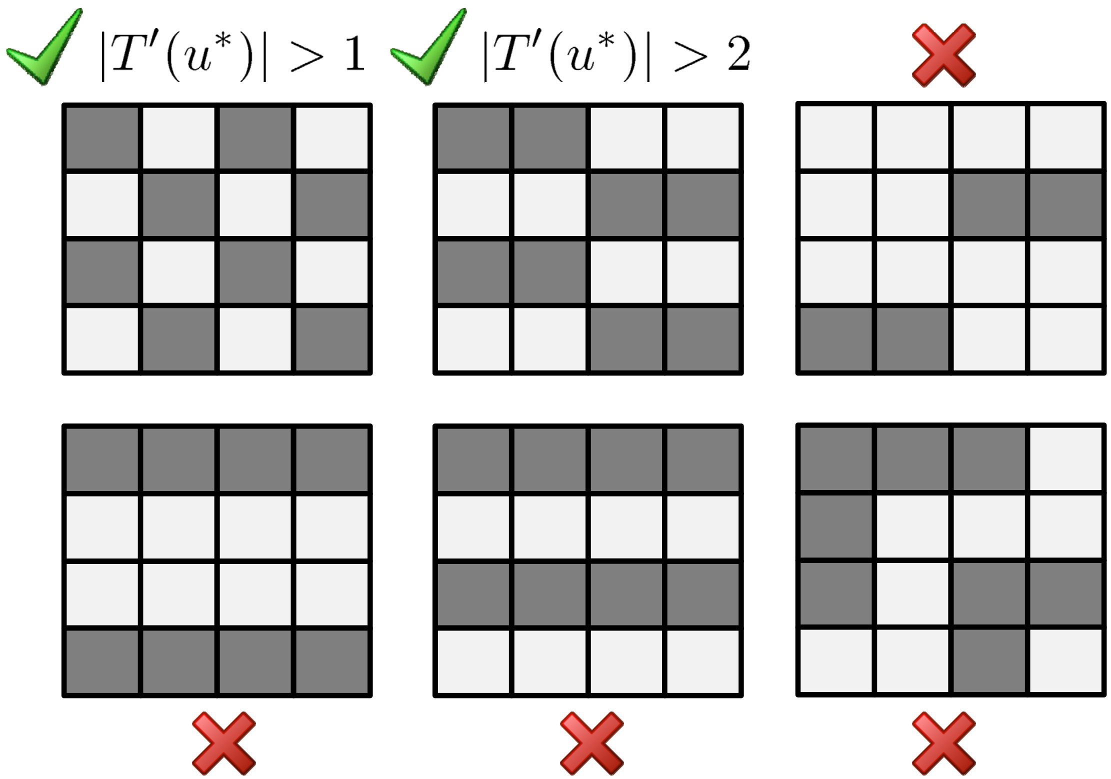
$N = 41$

Two-Dimensional Mesh with Wrap-Arounds:

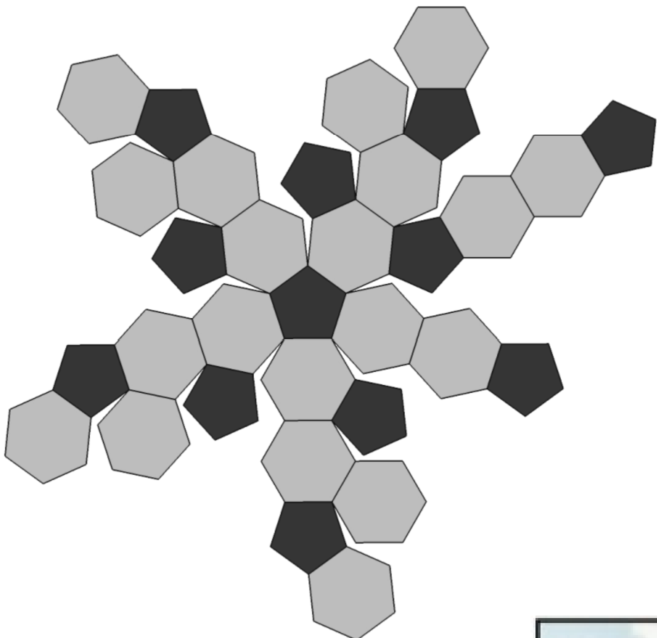


226 distinct equitable partitions identified from symmetries.

Theorem above applied to those with only two orbits:



Buckminsterfullerene Graphs:

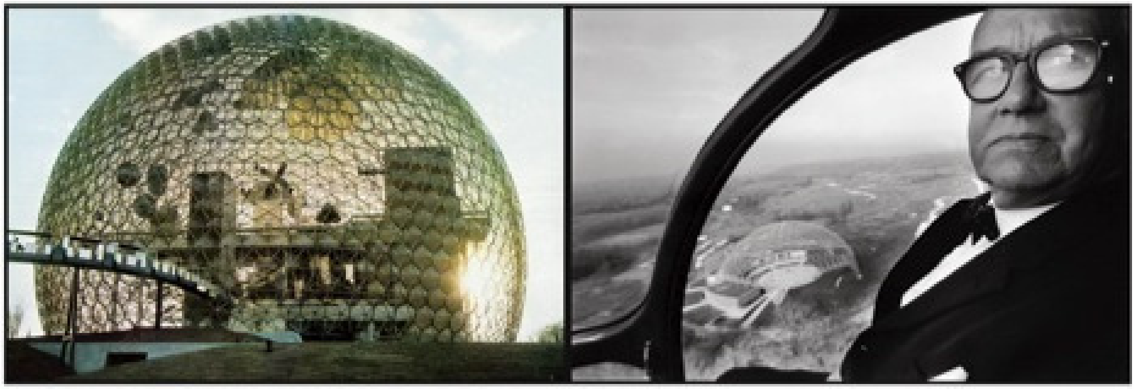


32 faces, interpreted as graph vertices.

Full automorphism group has two orbits:

O_1 : {12 pentagons}, O_2 : {20 hexagons}

Theorem above confirms "soccerball pattern" for $|T'(u^*)| > 2$



Buckminster Fuller (1895-1983)

Current Research Topics

- Relaxing the assumptions of the theorem (*e.g.*, bipartite reduced graph)
- Characterizing the stability and domain of attraction of the patterns
- Generic convergence to patterns proven for bipartite graphs.[5]
  Can other graphs exhibit complex dynamics?
- Application: A synthetic multi-cellular patterning system…

[5] Arcak, "Pattern formation by lateral inhibition: An analysis applicable to large scale networks of cells." Submitted.

Acknowledgment:

Ana Ferreira, Katia Nepomnyashchaya, NSF, AFOSR