Patterns in complexity: from network topology to phenotypic landscape

APS SATELLITE MEETING
15/03/2022

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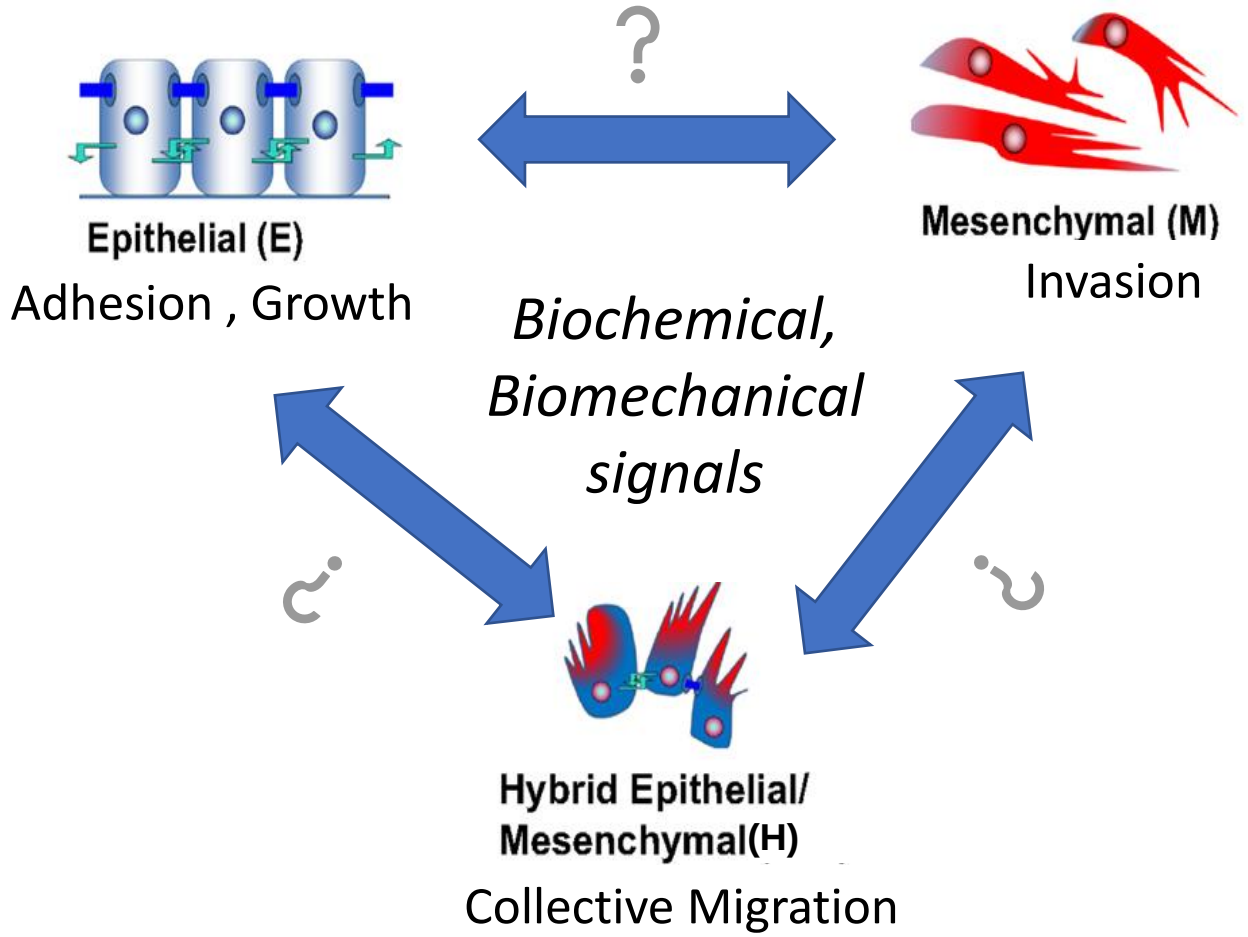
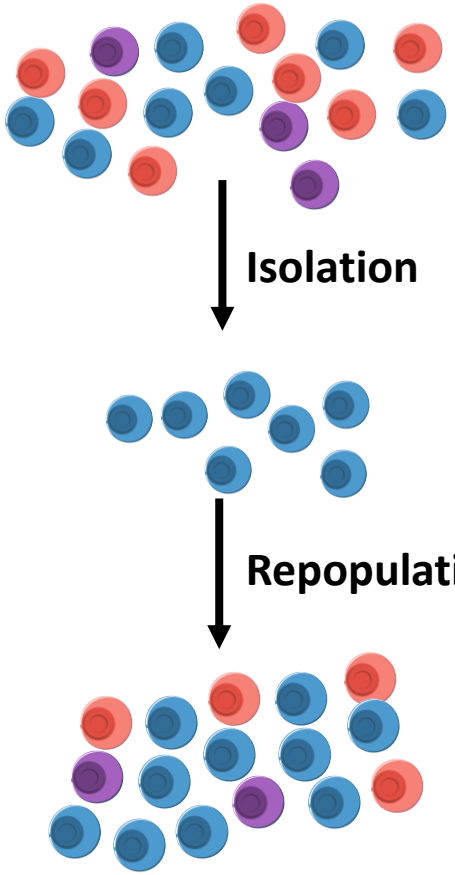
Epithelial Mesenchymal Plasticity

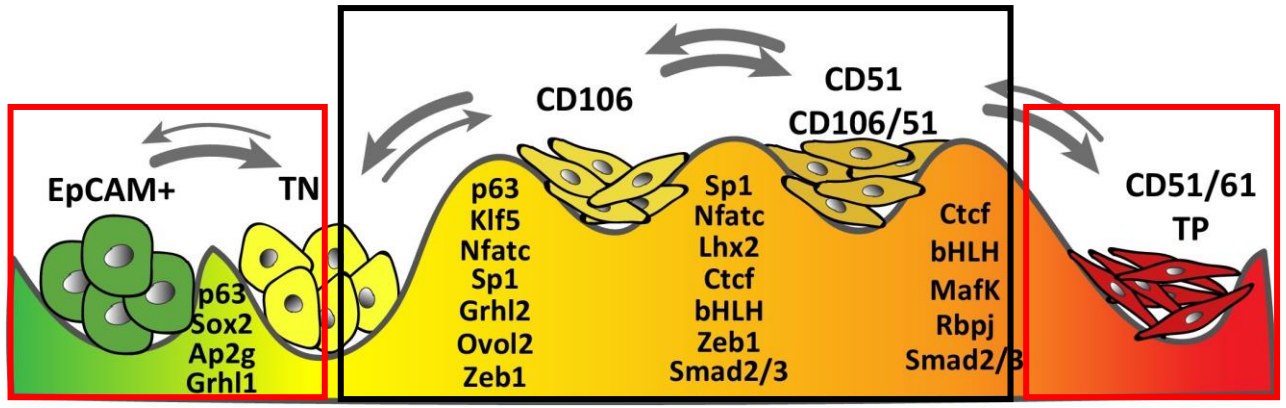


- Reversible switching between three classes of phenotypes
- Switches triggered by biochemical/biophysical signals
- Multistability increases chances of cell survival
- **What do the switching dynamics look like?**

Epithelial-Mesenchymal Plasticity (EMP)

The EMP phenotypic stability "landscape"





	Epithelial tumor cells	Early hybrid EMT state	Hybrid EMT state	Late hybrid EMT state	Mesenchymal tumor cells
Proliferation	+++++	++++	+++	++	+
Invasion	+	++	+++	++++	+++++
Plasticity	+	++	+++	++++	++
Stemness	+	+++	+++	+++	+++
Metastasis	+	++++	++++	++	+

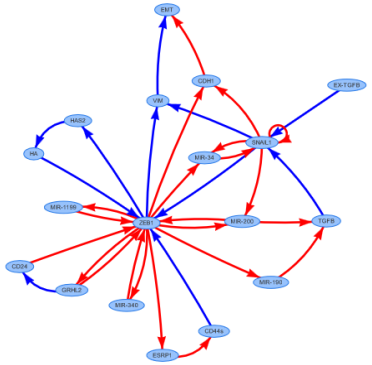
The Terminal phenotypes are more "stable" than the Hybrid phenotypes

Can regulatory networks explain the stability patterns?

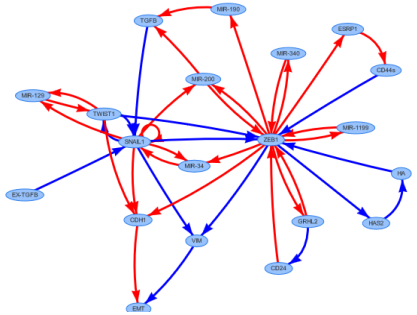
Pastushenko I *et al*., Nature 2018

Pastushenko I, Blanpain C, Trends Cell Biol 2019

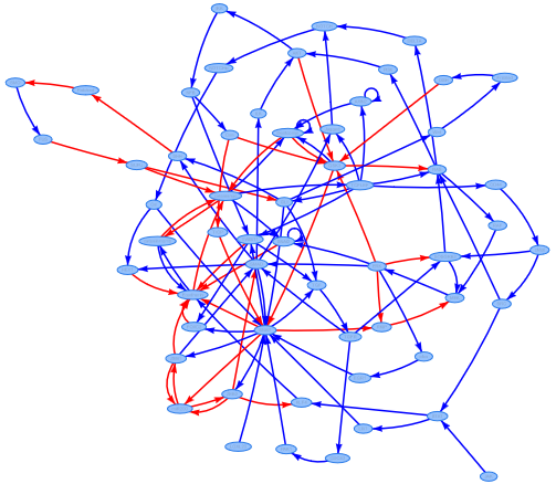
Gene Regulatory networks underlying EMP



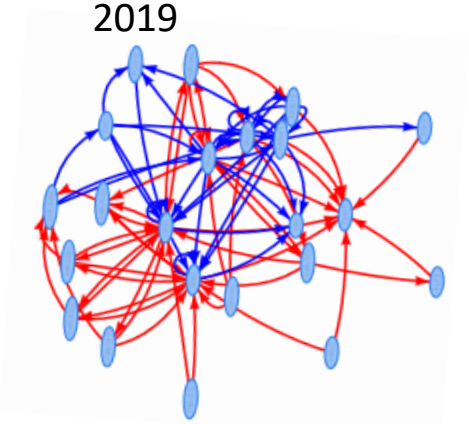
Silveira D A, Mombach J C M, 2019



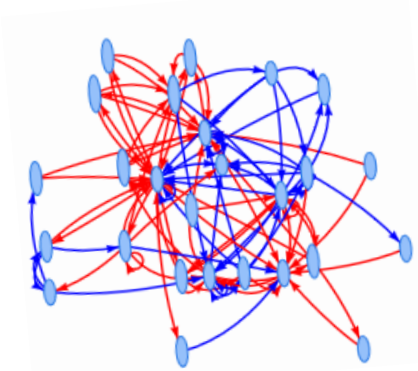
Silveira D A *et al.*, 2019



Font-clos *et al.*, 2018



Huang B *et al*, 2017

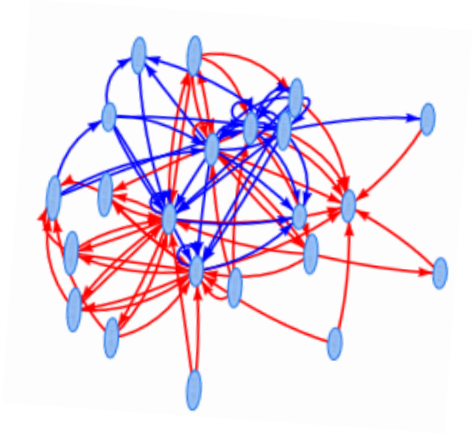


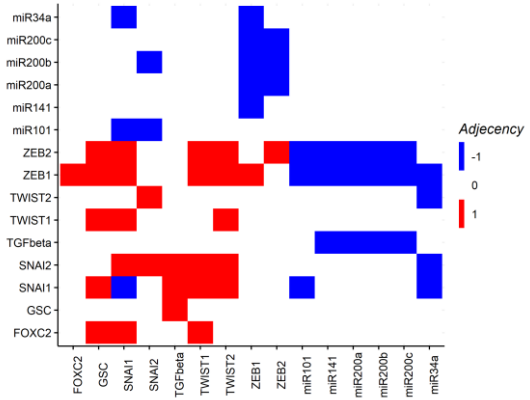
Tripathi S *et al.*, 2020

Can the dynamics of EMP networks result in the observed stability landscape?

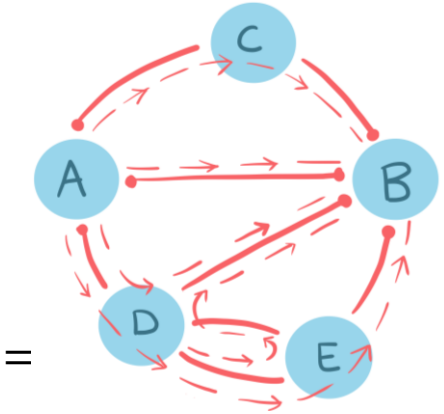
Hypothesis: Underlying regulatory networks can explain a)multistability and b)switching dynamics of EMP

Influence matrix shows two teams of nodes





Adjacency matrix (Adj)



$$I_{A\to B} = \frac{B}{-}, \ldots.)$$

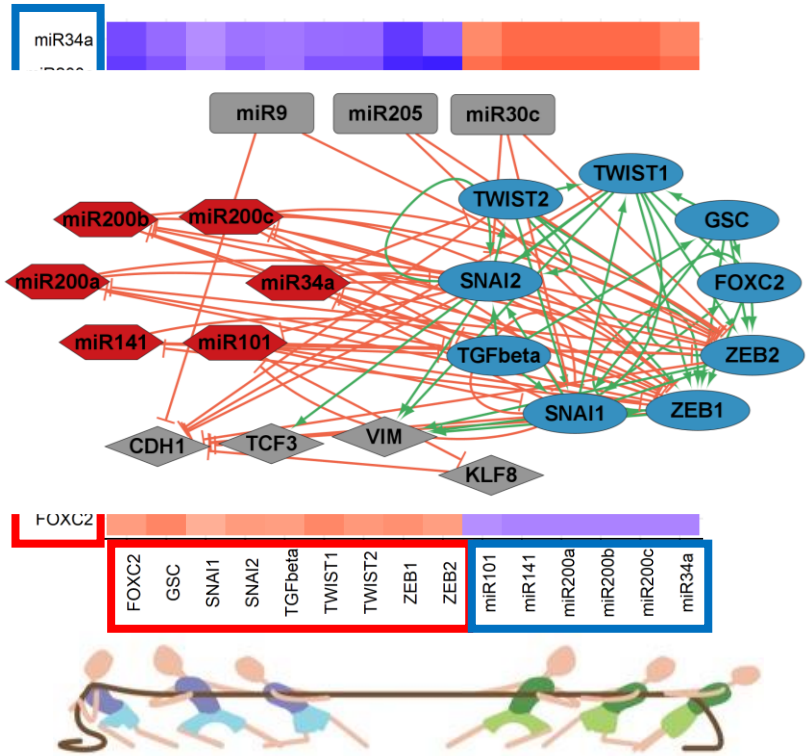
$$Infl = \frac{\sum_{l=1}^{lmax} \frac{Adj^l}{Adj_{max}^l}}{lmax}$$

$Infl : Influence\ Matrix\ (right)$

$Adj : Adjecency\ Matrix\ (left)$

$$Adj_{max}(i,j) = \begin{cases} 1, & Adj(i,j) = -1 \\ Adj(i,j), & Adj(i,j) \neq -1 \end{cases}$$

Influence matrix (Infl)



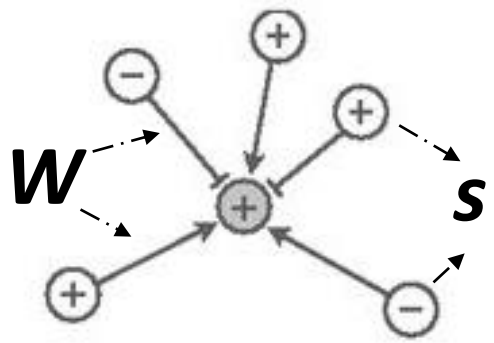
Do teams direct the stability of phenotypes?

Epithelial Mesenchymal

Chauhan L *et al*., eLife, 2021

Steady states of EMP networks

Boolean dynamics



$$s_i(t+1) = \sum_{j \in I_i} W_{ji} s_j(t)$$

$s_i = \pm 1$

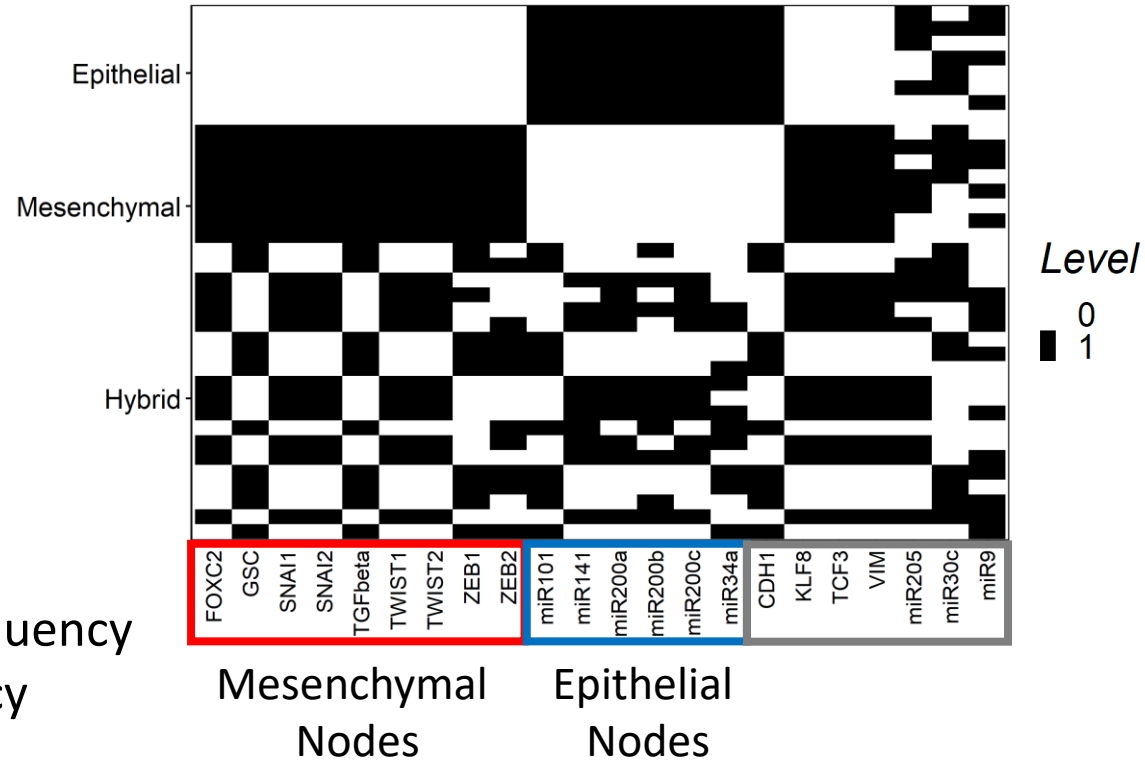
$W_{ji} = \pm 1$

I_i : *Input nodes to i*

Simulate for 100000 random initial states, n = 3

Steady states

$S(t+1) = S(t)$



Epi + Mes phenotypes : 95% frequency

Hybrid phenotypes: 5% frequency

Mesenchymal Nodes

Epithelial Nodes

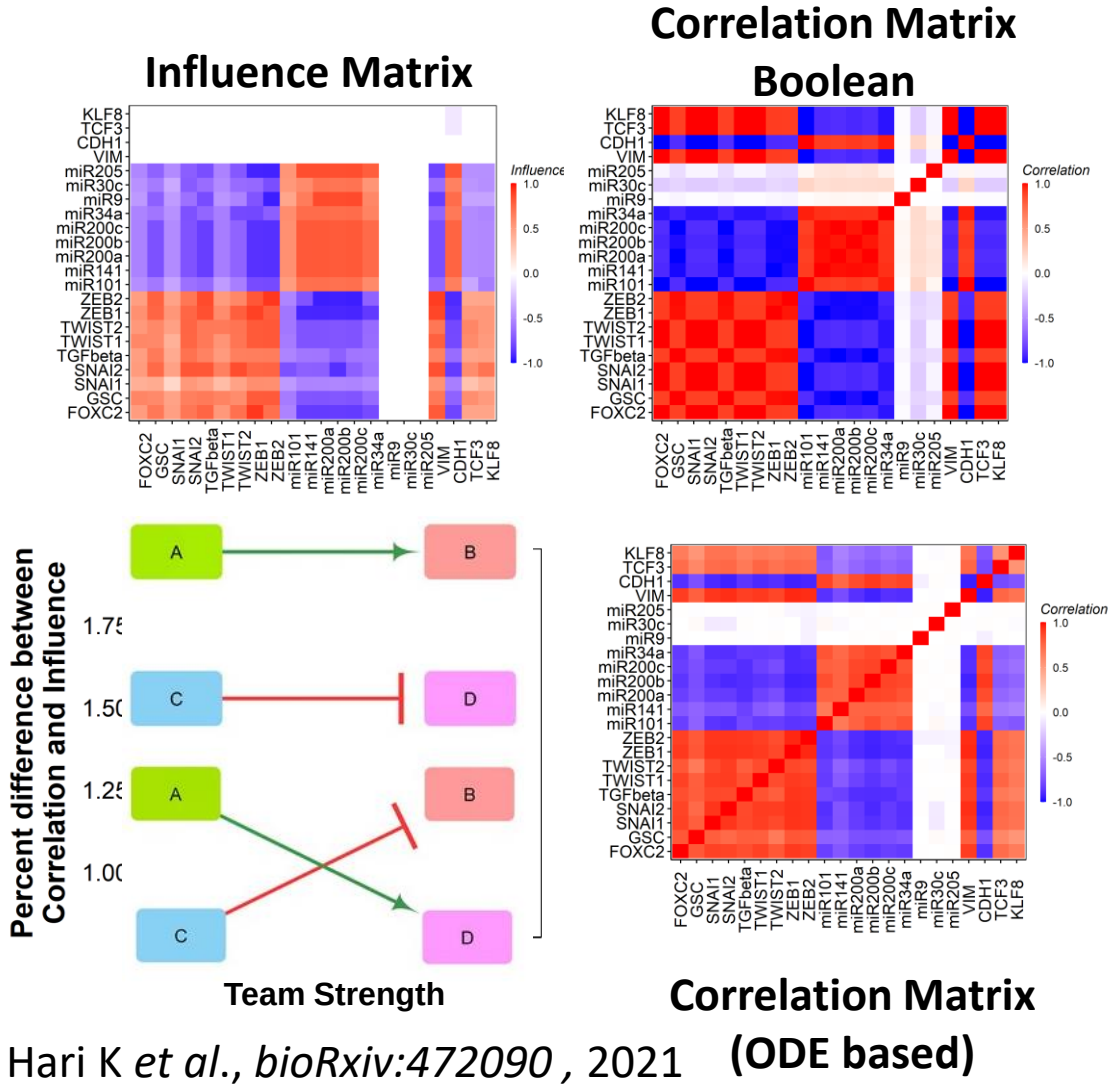
State configuration agrees with team configuration

Font-clos *et al.*, PNAS, 2018

Shomar *et al.*, Plos One, 2020

Hari *et al.*, *bioRxiv:472090* , 2021

Similarity between influence and correlation matrices



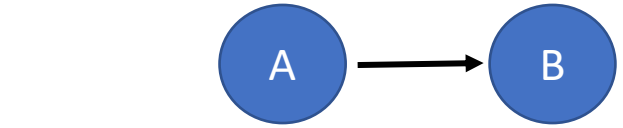
$$PercentDiff = 100 * \sum_{i,j<N} \frac{|Infl_{ij} - Cor_{ij}|}{2 * N}$$

- The difference between influence matrix and correlation matrix is <3%, for WT as well as random networks!
- The similarity holds for RACIPE simulations as well
- **Influence matrix can indicate the most dominant phenotypes of a network without any simulations**

Hari K *et al.*, *bioRxiv:472090* , 2021

Static and dynamic stability of EMP phenotypes

How well is a state supported by the network?



$W_{ij}s_is_j > 0$ ON ON

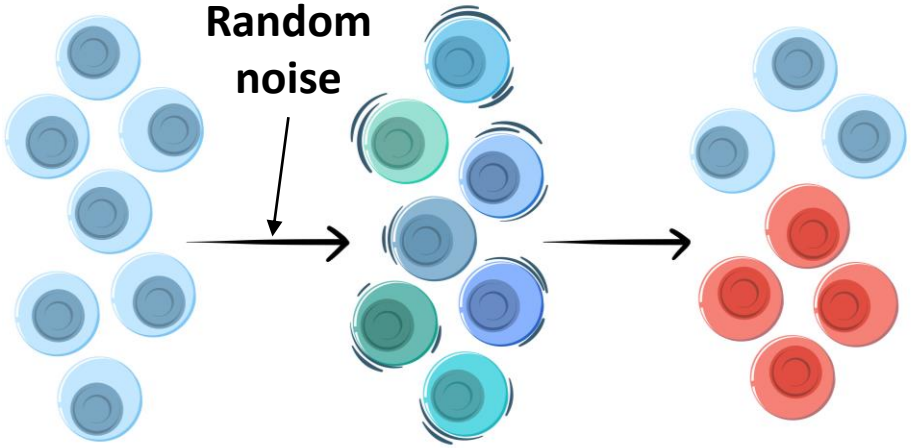
$\boldsymbol{W_{ij}s_is_j < 0}$ ON OFF

$$\textbf{Frustration} = \frac{E_f}{E_t}$$

E_f: number of frustrated edges

E_t: total number of edges

How well is a phenotype maintained against dynamic perturbations (change in node expression level)?

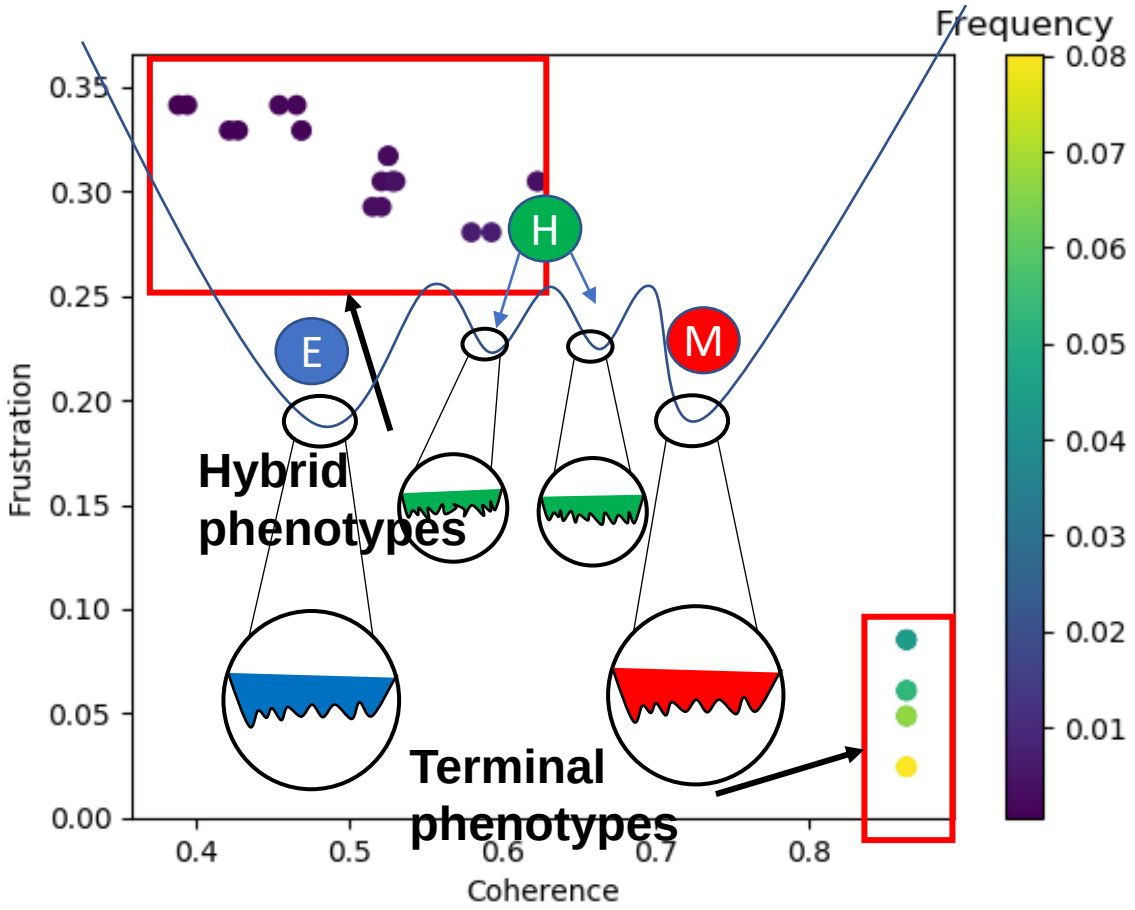


Coherence = fraction of retention upon perturbation

Does the stability landscape agree with experimental observations?

Hari K *et al.*, *bioRxiv:472090* , 2021
Tripathi S *et al.*, Phys Rev Lett, 2020

Simulated phenotypes show expected stability landscapes

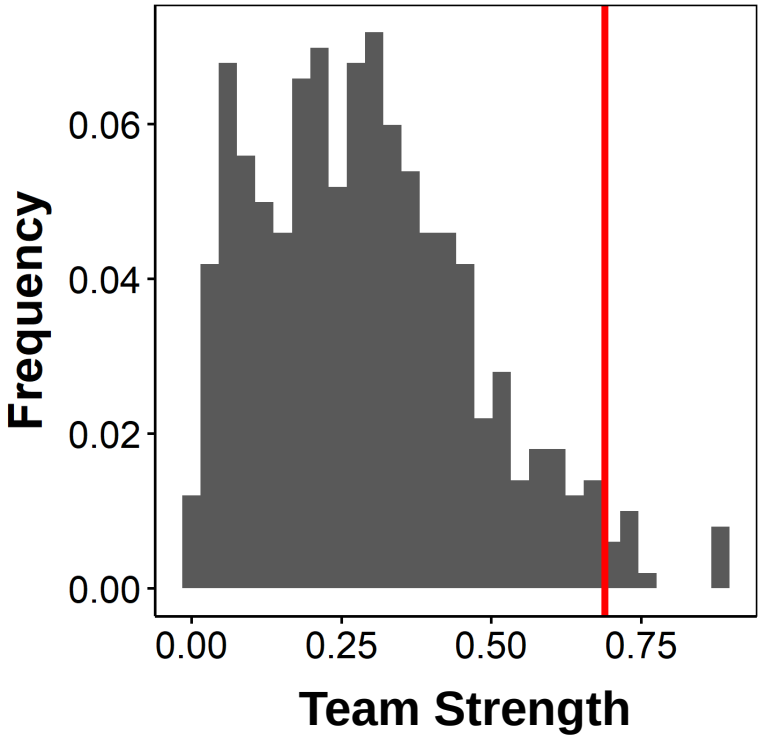


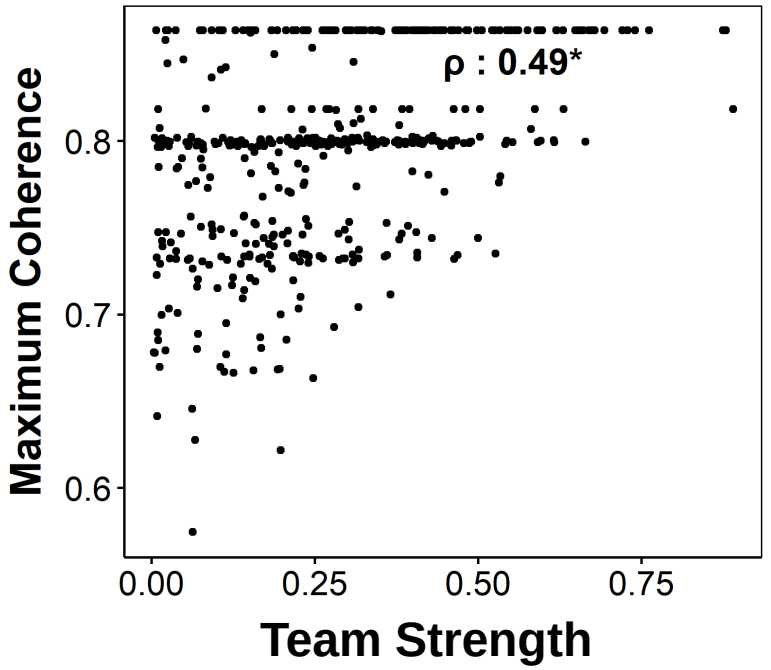
36 (micro)states; 3 phenotypes (macro-states)

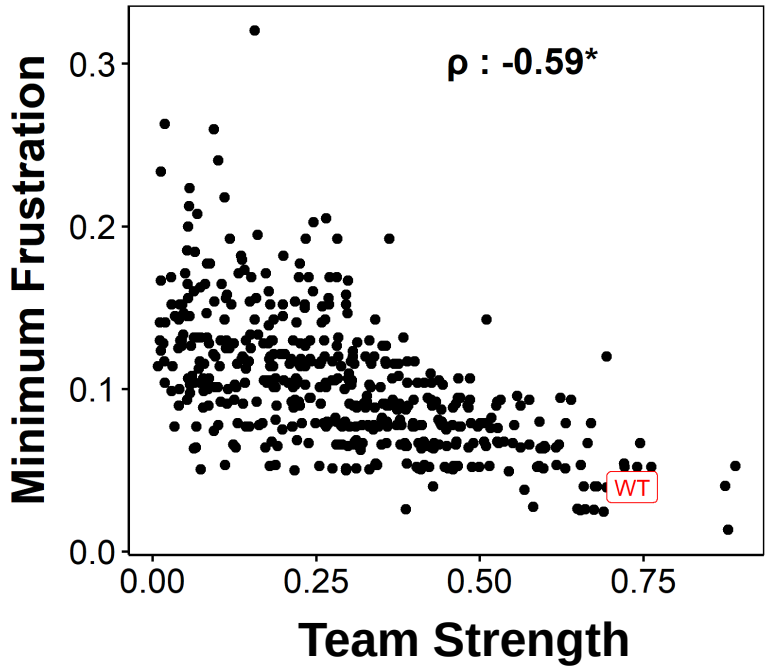
- High stability = high steady state frequency (SSF) = high coherence = low frustration
- Terminal phenotypes show high static and dynamic stability
- Topology alone can qualitatively replicate experimental landscape
- **Do teams stabilize terminal phenotypes?**

Hari K *et al.*, *bioRxiv:472090* , 2021

Strong teams => highly stable terminal phenotypes



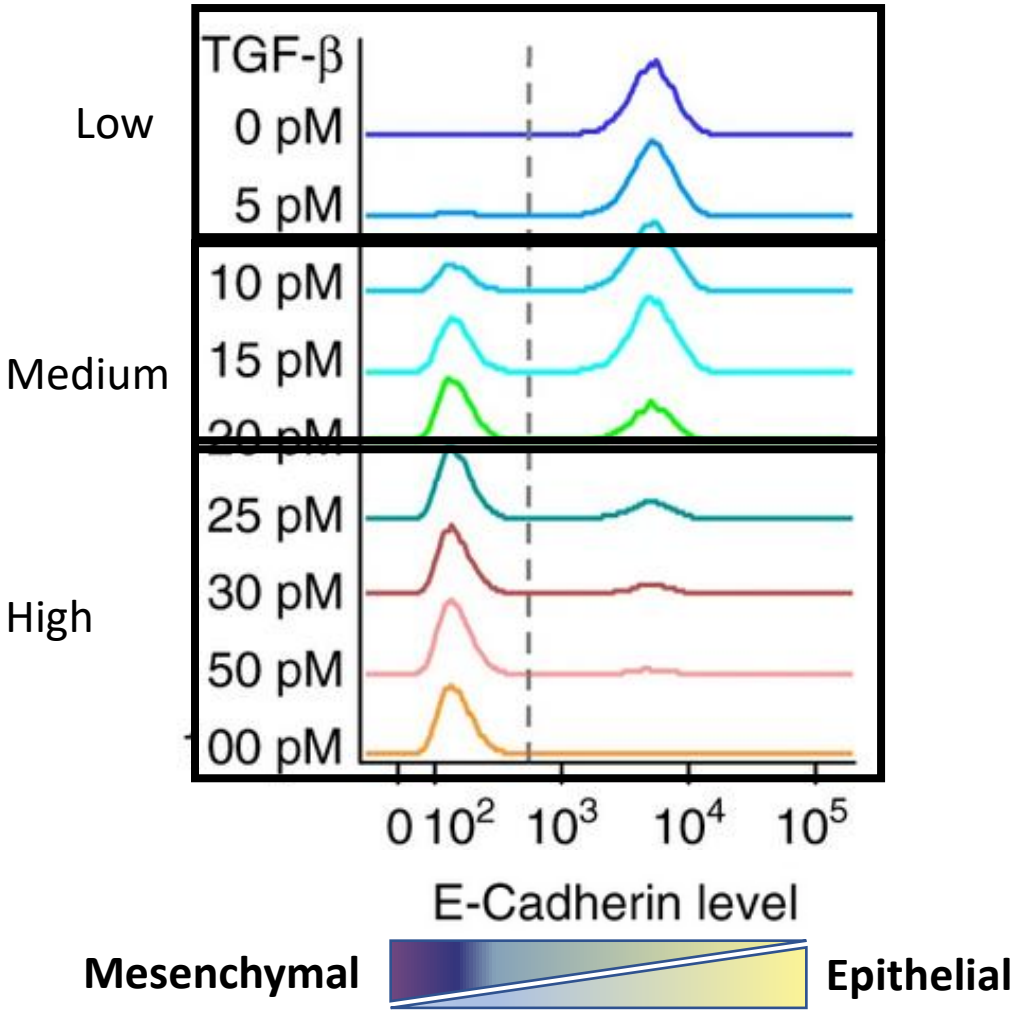




As teams weaken, the stability patterns become widely distributed

Hari *et al.*, *bioRxiv:472090* , 2021

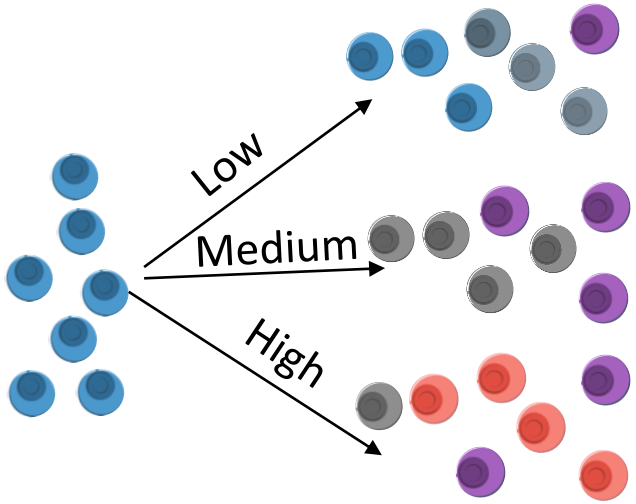
Phenotypic transition in EMP

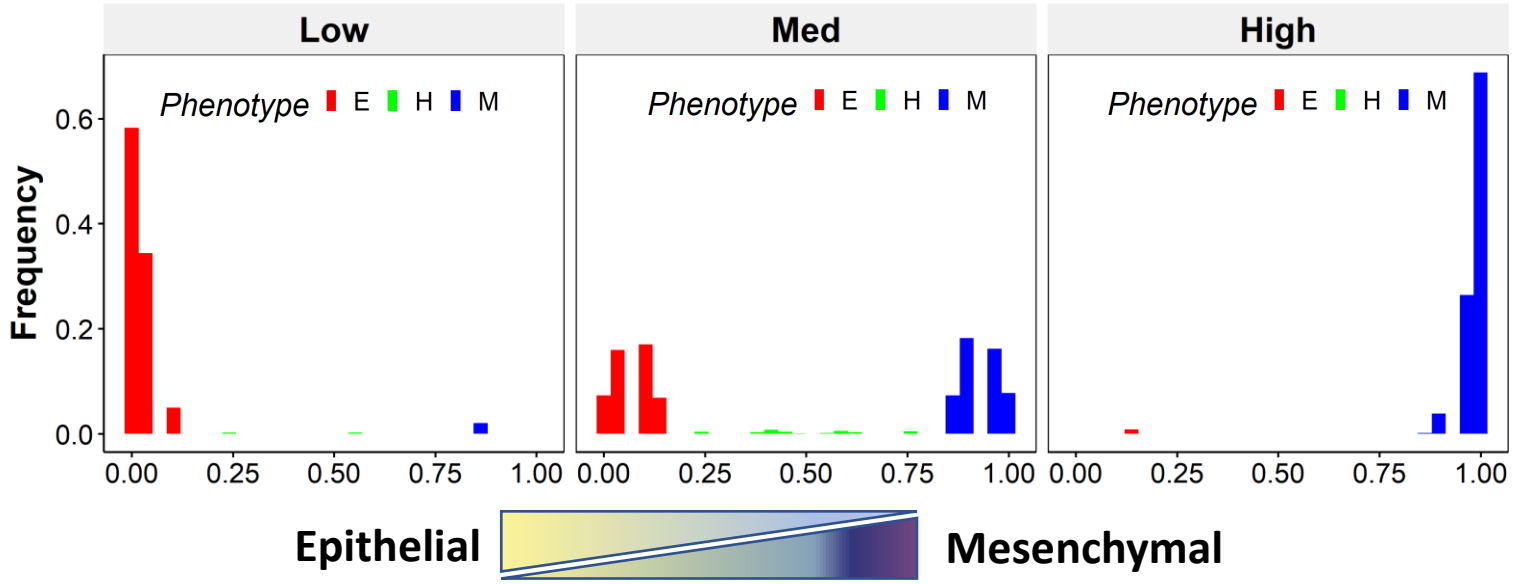


Celia-Terrassa T *et al.*, Nat. Comm., 2018

- Low levels of TGF-b, population is dominantly epithelial
- High levels of TGF-b, population is dominantly mesenchymal
- Medium levels of TGF-b, bimodal population
- **Can these trends be explained by teams?**

EMP networks show expected transition dynamics



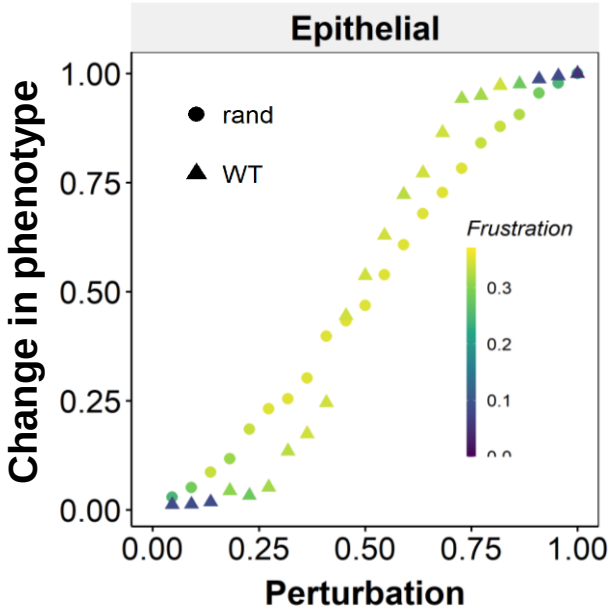


Perturbation = fraction of nodes whose expression level has been changed

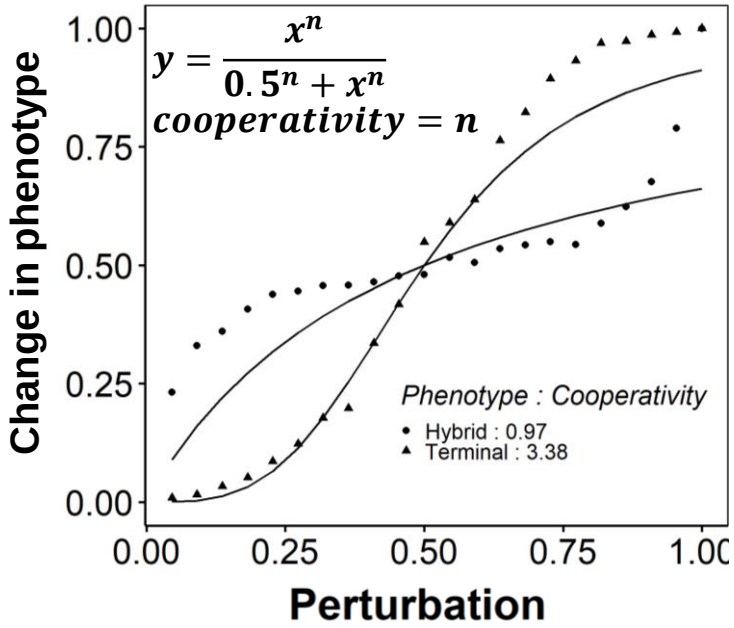
Small set of uniqueperturbations can switch the phenotype

Hari K *et al.*, *bioRxiv:472090* , 2021

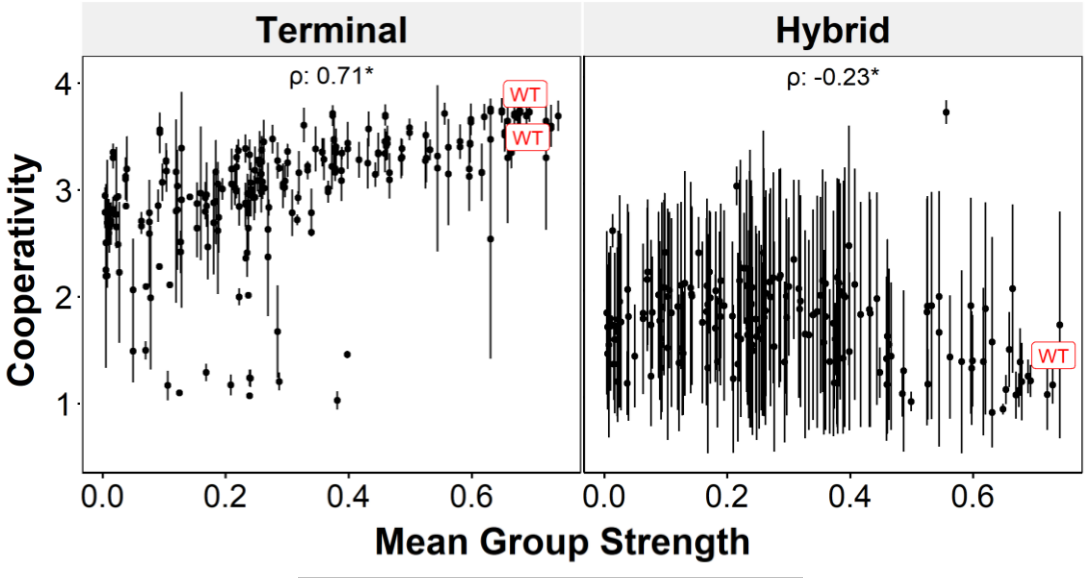
Weak teams => loss of distinct transition dynamics



Network with weak teams loses sigmoidal transition



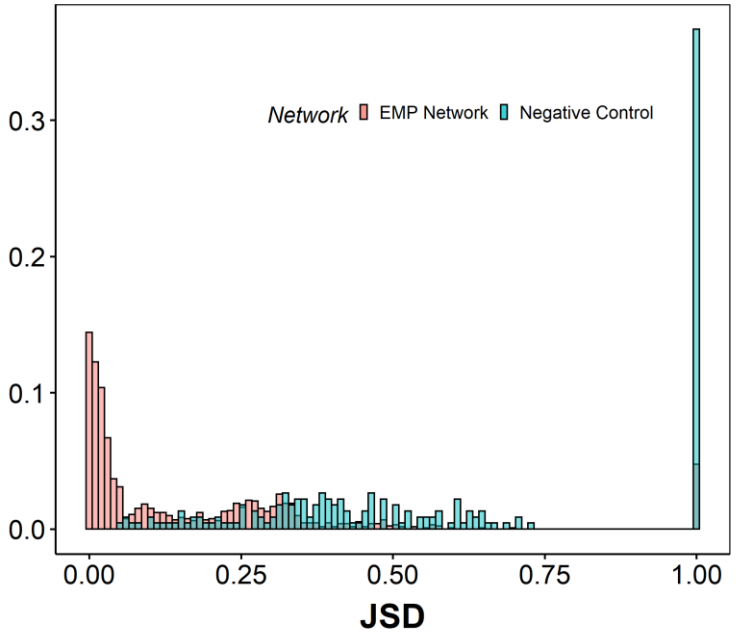
Fit the transition curves to sigmoid, obtain cooperativity measures



Teams support sigmoidal transition of terminal phenotypes

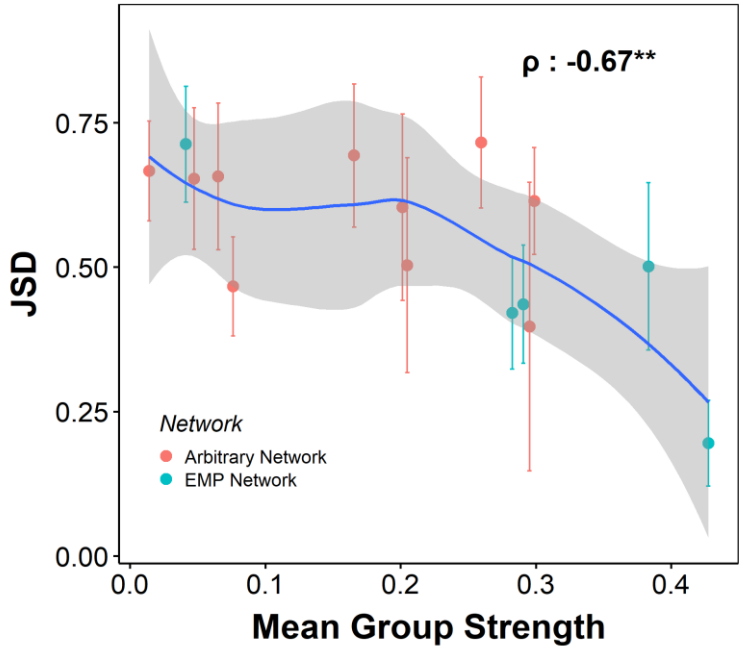
Hari *et al.*, *bioRxiv:472090* , 2021

Teams provide structural robustness



Networks with weak teams show higher JSD

$W_{AB} \in [-1,1]$

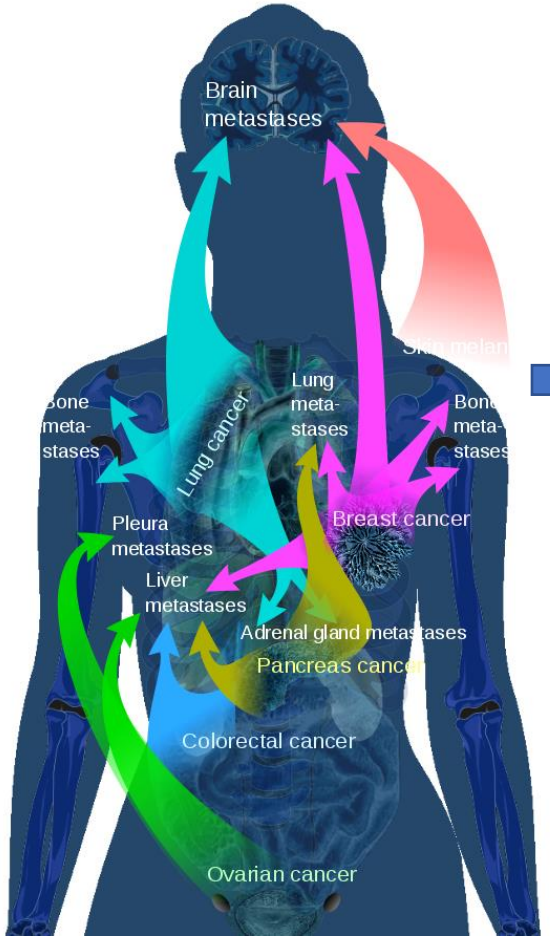


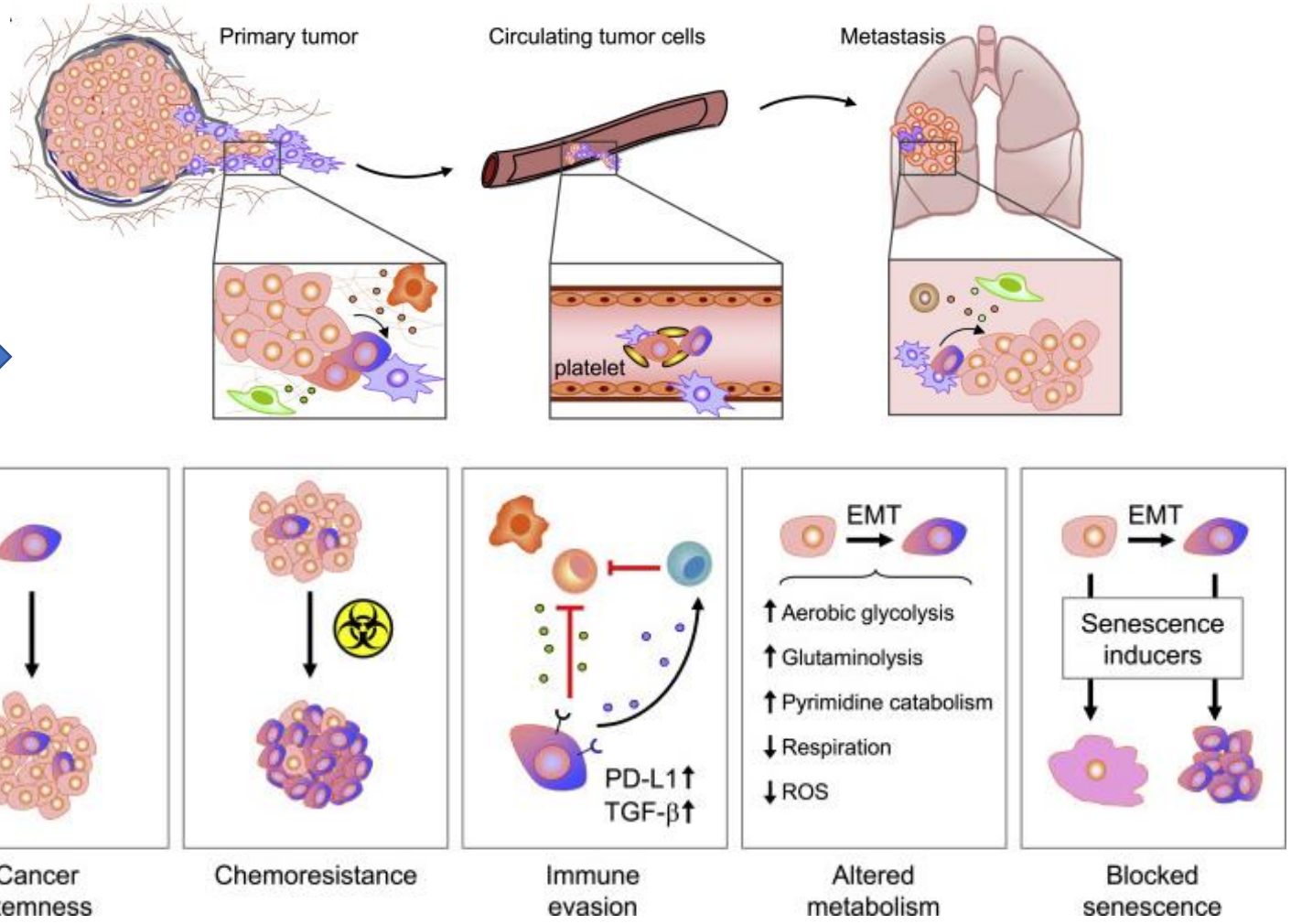
Groups provide robustness against global perturbations in edge strengths

Summary

- EMP networks are designed to have teams of nodes
- Strong teams lead to stable terminal phenotypes
- Terminal phenotypes and hybrid phenotypes show unique dynamic characteristics, which are lost when teams weaken.
- Teams provide robustness against biochemical noise (node perturbation) and mutations (edge perturbation)

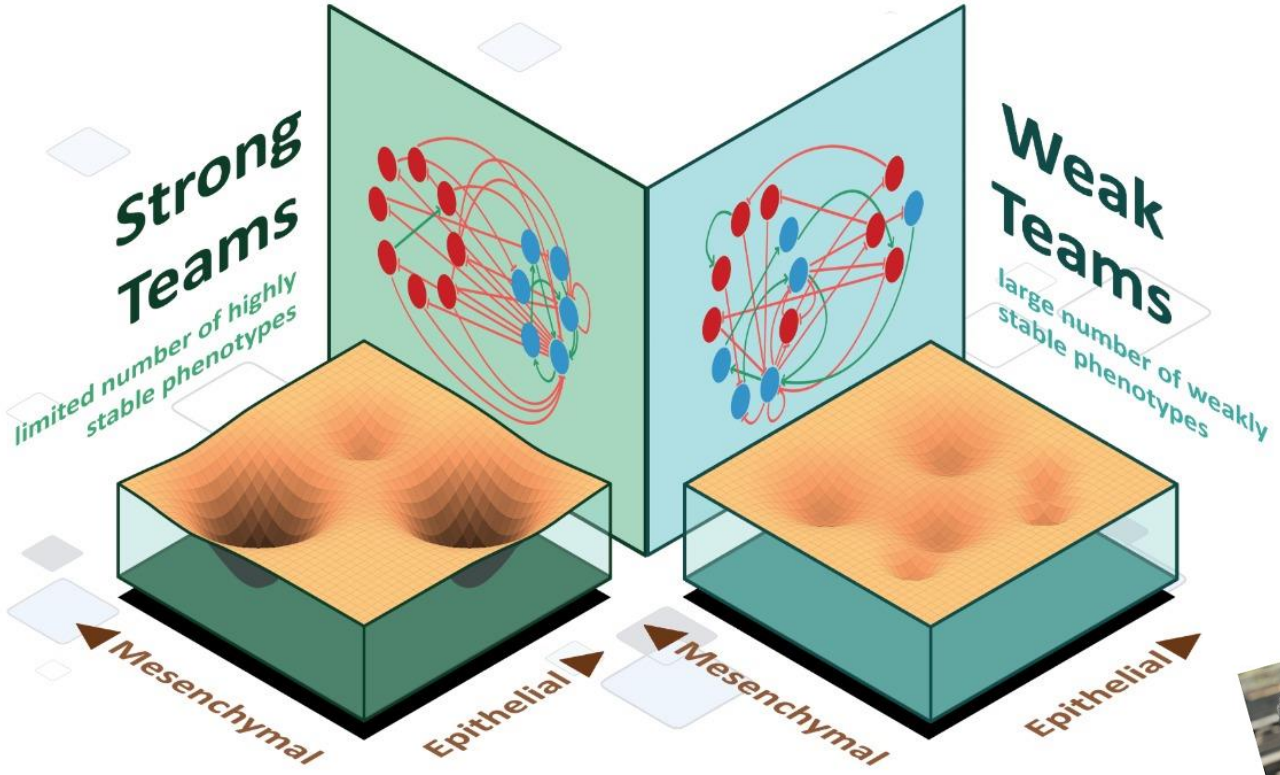
Metastatic cells can adapt to various challenges





Celià-Terrassa T, Kang Y, Genes Dev, 2016
Lu W, Kang Y, Developmental Cell, 2019

What other patterns in complex networks?



Varun Ullanat
Aditi Gopalan
Archana Balasubramanian
Dr. Mohit Kumar Jolly

Picture Credit (This and the other good looking Images in the presentation): **Atchuta**

Thank you for your attention!

Questions ?