Why Biology is Different

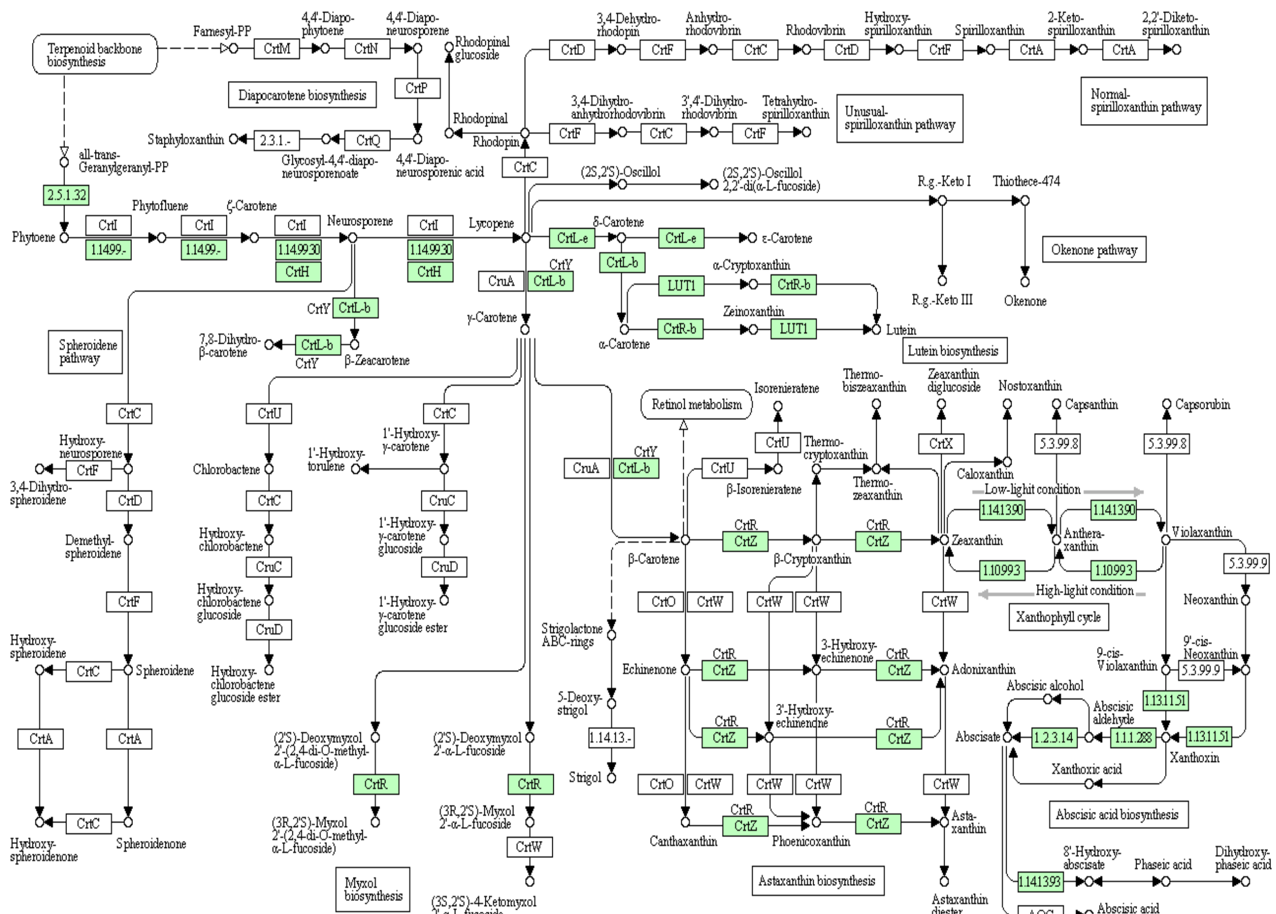
Bernard Chazelle

Princeton University

On leave at Collège de France

and Institute for Advanced Study

$$\frac{\partial T}{\partial t} = D\,\Delta T$$



PDE

Natural algorithm

PDE

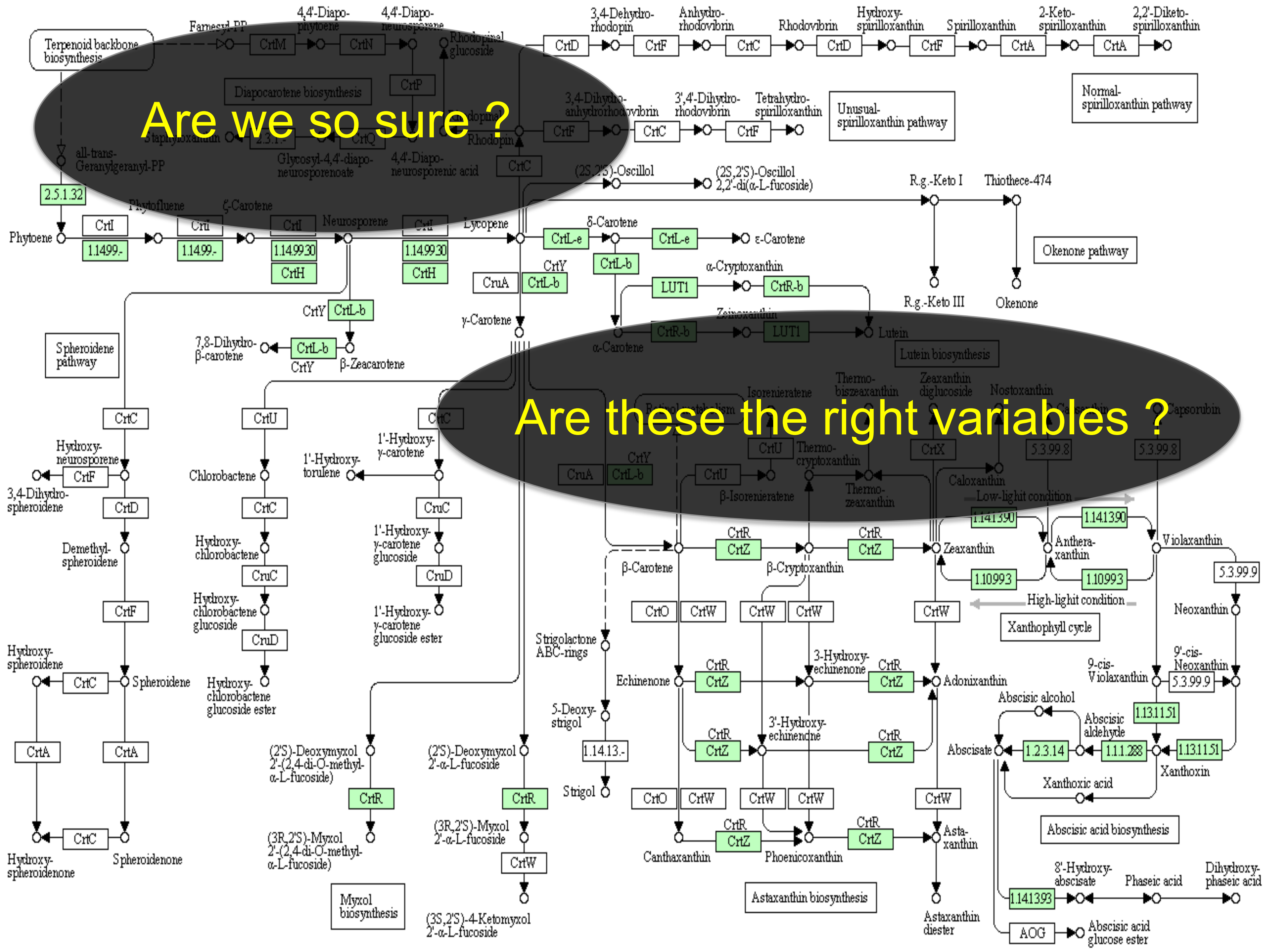
Natural algorithm

loops, conditionals, memory…

PDE

Natural algorithm

not human-designed


Are we so sure ?
Are these the right variables ?
Terpenoid backbone biosynthesis
Farnesyl-PP
4,4'-Diapo-phytoene
4,4'-Diapo-neurosporene
CrtM
CrtN
CrtP
Rhodopinal glucoside
Diapocarotene biosynthesis
all-trans-Geranylgeranyl-PP
Glycosyl-4,4'-diapo-neurosporenoate
4,4'-Diapo-neurosporenic acid
3,4-Dehydro-rhodopin
Anhydro-rhodovibrin
Rhodovibrin
Hydroxy-spirilloxanthin
Spirilloxanthin
2-Keto-spirilloxanthin
2,2'-Diketo-spirilloxanthin
CrtD
CrtF
CrtC
CrtA
Normal-spirilloxanthin pathway
3,4-Dihydro-anhydrorhodovibrin
3',4'-Dihydro-rhodovibrin
Tetrahydro-spirilloxanthin
Unusual-spirilloxanthin pathway
Rhodopin
(2S,2'S)-Oscillol
(2S,2'S)-Oscillol 2,2'-di(α-L-fucoside)
R.g.-Keto I
Thiothece-474
R.g.-Keto III
Okenone
Okenone pathway
2.5.1.32
Phytoene
Phytofluene
ζ-Carotene
Neurosporene
Lycopene
CrtI
1.14.99.-
1.14.99.30
CrtH
δ-Carotene
ε-Carotene
CrtL-e
CrtL-b
CrtY
CruA
α-Cryptoxanthin
LUT1
CrtR-b
γ-Carotene
Spheroidene pathway
7,8-Dihydro-β-carotene
β-Zeacarotene
Lutein
Lutein biosynthesis
CrtU
CruC
Hydroxy-neurosporene
3,4-Dihydro-spheroidene
Demethyl-spheroidene
Chlorobactene
Hydroxy-chlorobactene
Hydroxy-chlorobactene glucoside
Hydroxy-chlorobactene glucoside ester
CruD
1'-Hydroxy-γ-carotene
1'-Hydroxy-torulene
1'-Hydroxy-γ-carotene glucoside
1'-Hydroxy-γ-carotene glucoside ester
Isorenieratene
Thermo-biszeaxanthin
Zeaxanthin diglucoside
Nostoxanthin
Capsorubin
CrtX
5.3.99.8
Thermo-cryptoxanthin
Thermo-zeaxanthin
β-Isorenieratene
Caloxanthin
Low-light condition
1.14.13.90
Zeaxanthin
Anthera-xanthin
Violaxanthin
1.10.99.3
High-light condition
Xanthophyll cycle
5.3.99.9
Neoxanthin
β-Carotene
β-Cryptoxanthin
CrtR
CrtZ
CrtO
CrtW
Strigolactone ABC-rings
5-Deoxy-strigol
1.14.13.-
Strigol
Echinenone
3-Hydroxy-echinenone
Adonixanthin
3'-Hydroxy-echinenone
Canthaxanthin
Phoenicoxanthin
Asta-xanthin
Astaxanthin diester
Astaxanthin biosynthesis
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Spheroidene
Spheroidenone
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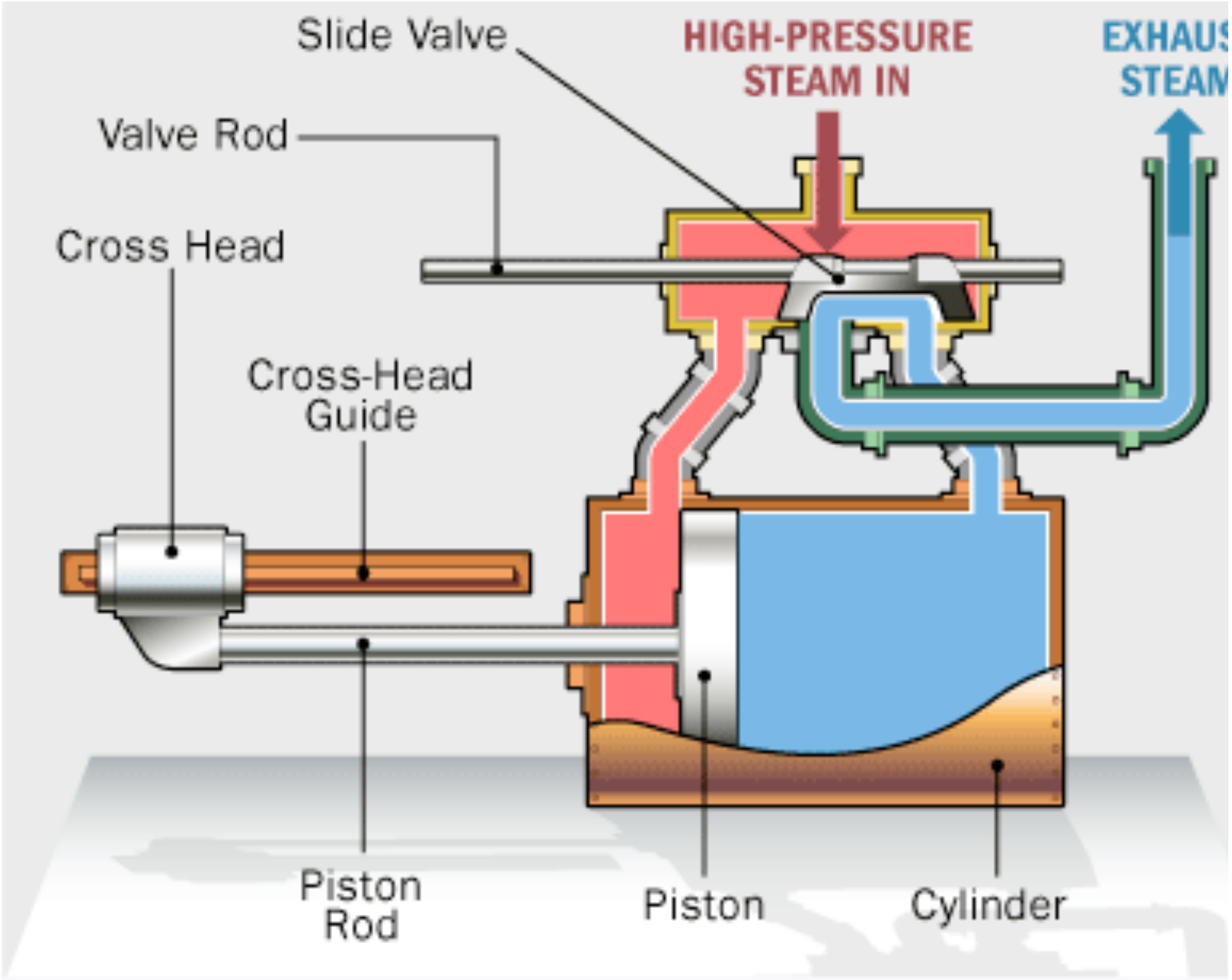
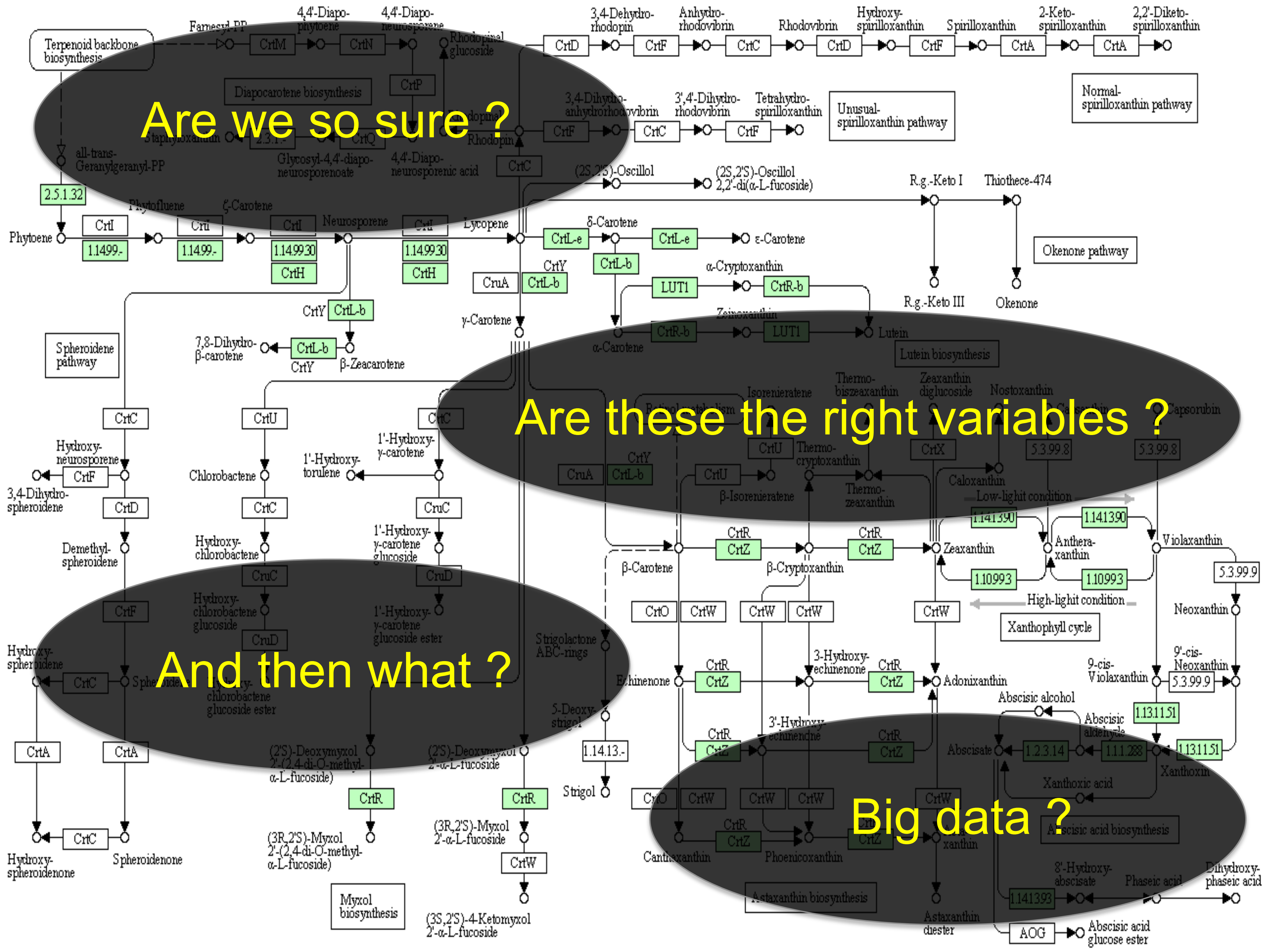
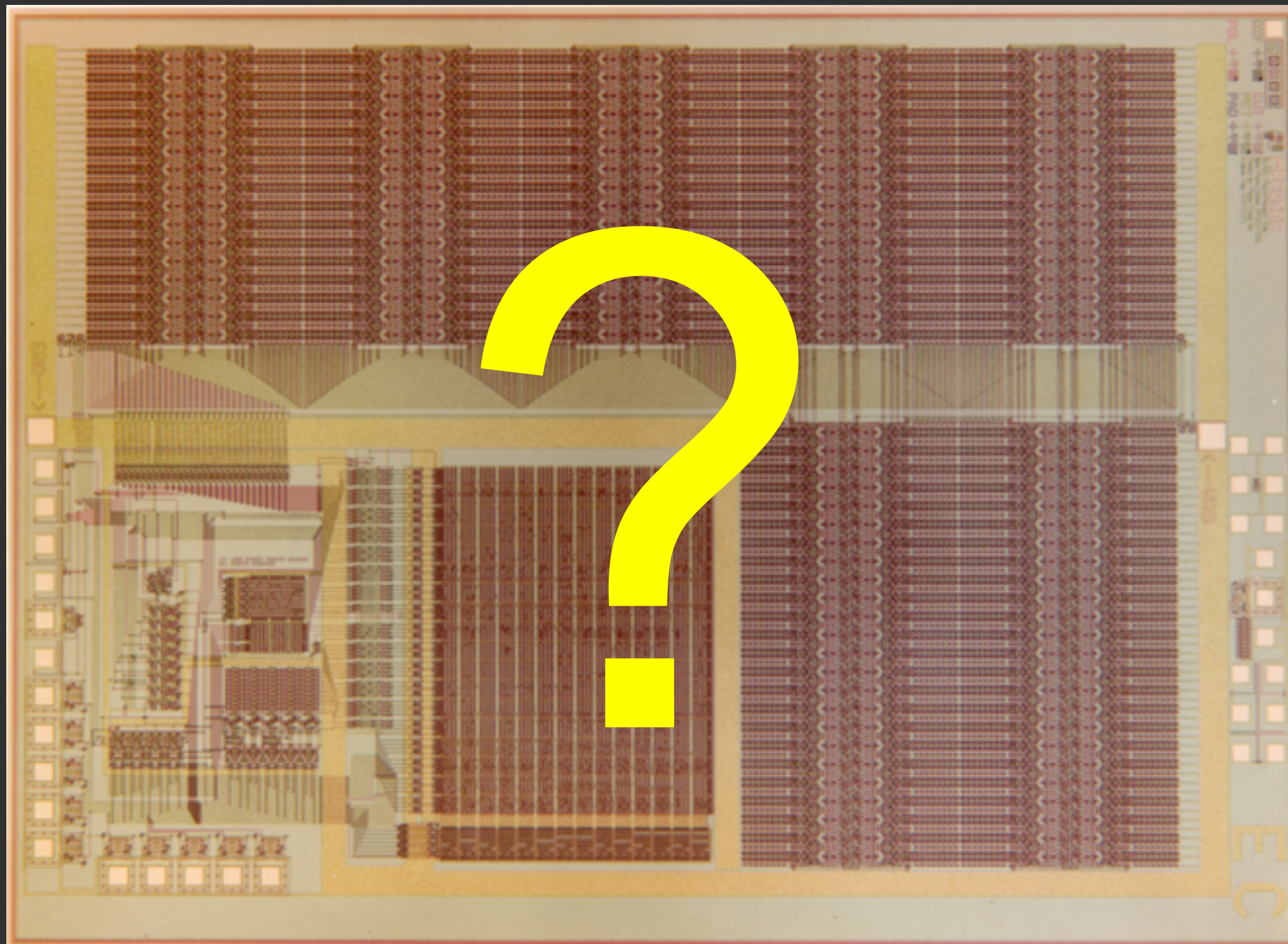
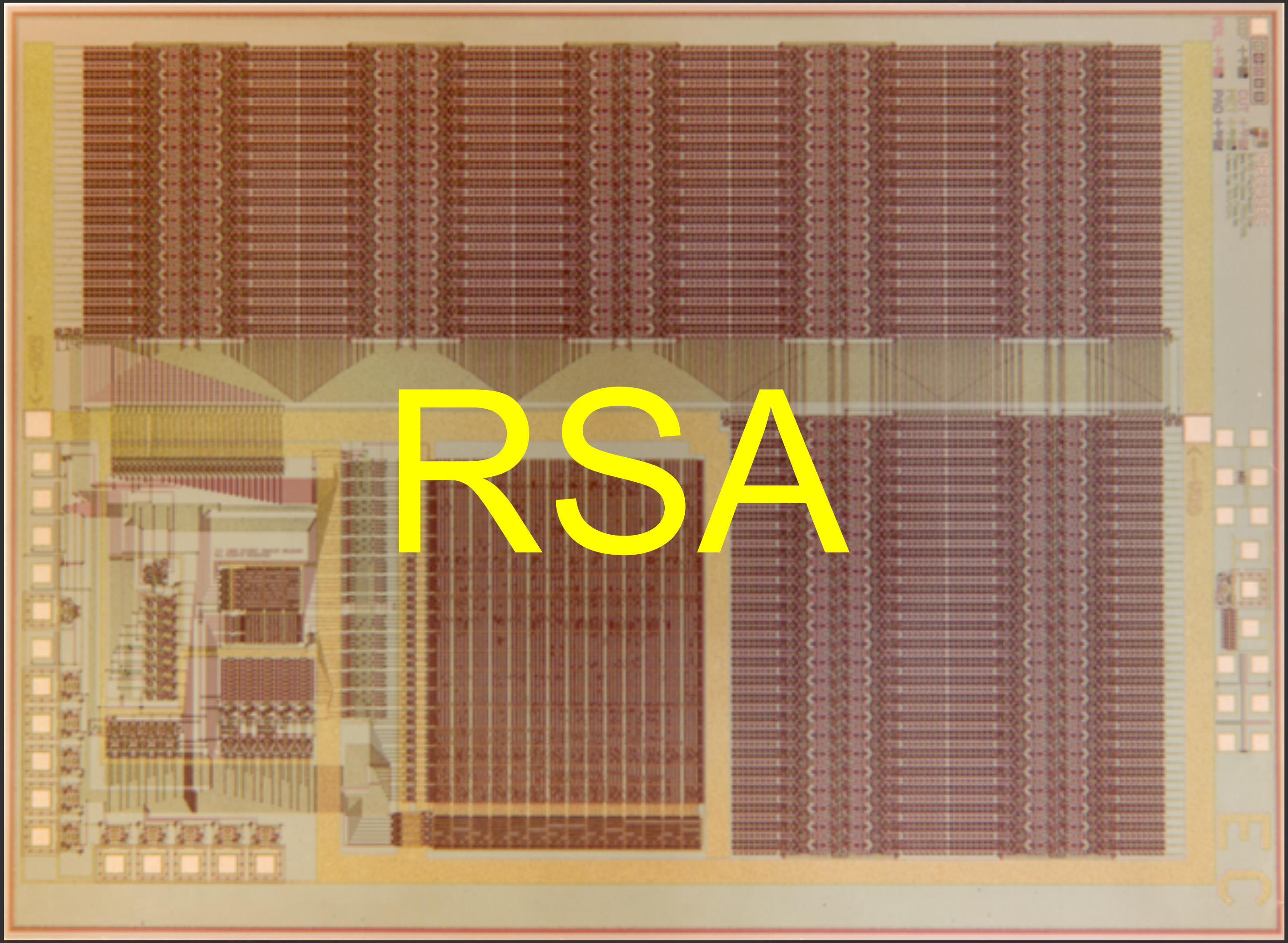
(3R,2'S)-Myxol 2'-(2,4-di-O-methyl-α-L-fucoside)
(3R,2'S)-Myxol 2'-α-L-fucoside
(3S,2'S)-4-Ketomyxol 2'-α-L-fucoside
Myxol biosynthesis
9-cis-Violaxanthin
9'-cis-Neoxanthin
1.13.11.51
Abscisic alcohol
Abscisic aldehyde
Abscisate
1.2.3.14
1.1.1.288
Xanthoxin
Xanthoxic acid
Abscisic acid biosynthesis
8'-Hydroxy-abscisate
Phaseic acid
Dihydroxy-phaseic acid
1.14.13.93
AOG
Abscisic acid glucose ester


Slide Valve
HIGH-PRESSURE
STEAM IN
Valve Rod
Cross Head
Cross-Head
Guide
Piston
Rod
Piston
Cylinder

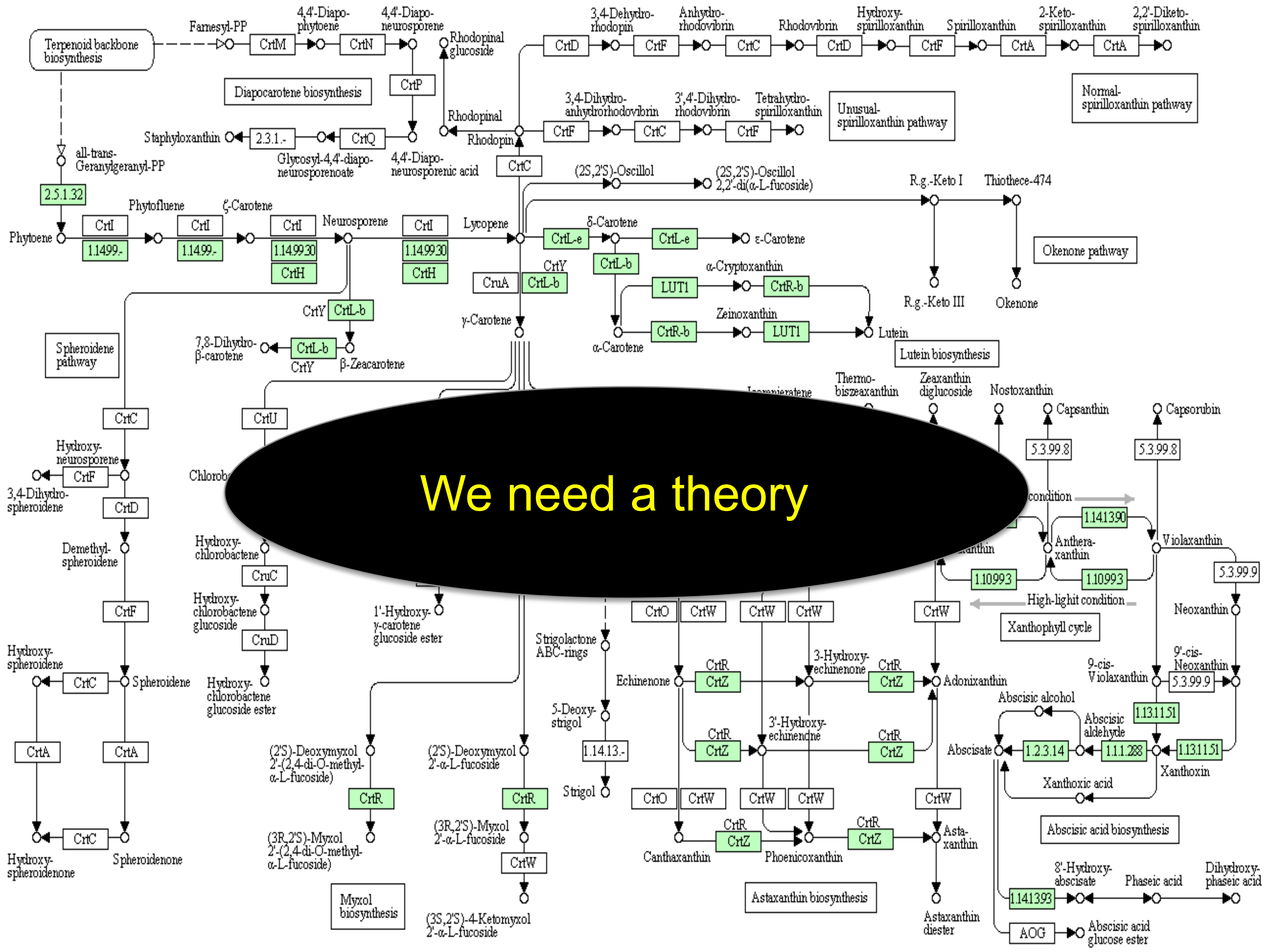
P, V, T, S, G


Are we so sure ?
Are these the right variables ?
And then what ?
Big data ?




RSA

Beware of Linear A



We need a theory
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AOG
Abscisic acid glucose ester

Mathematics ?

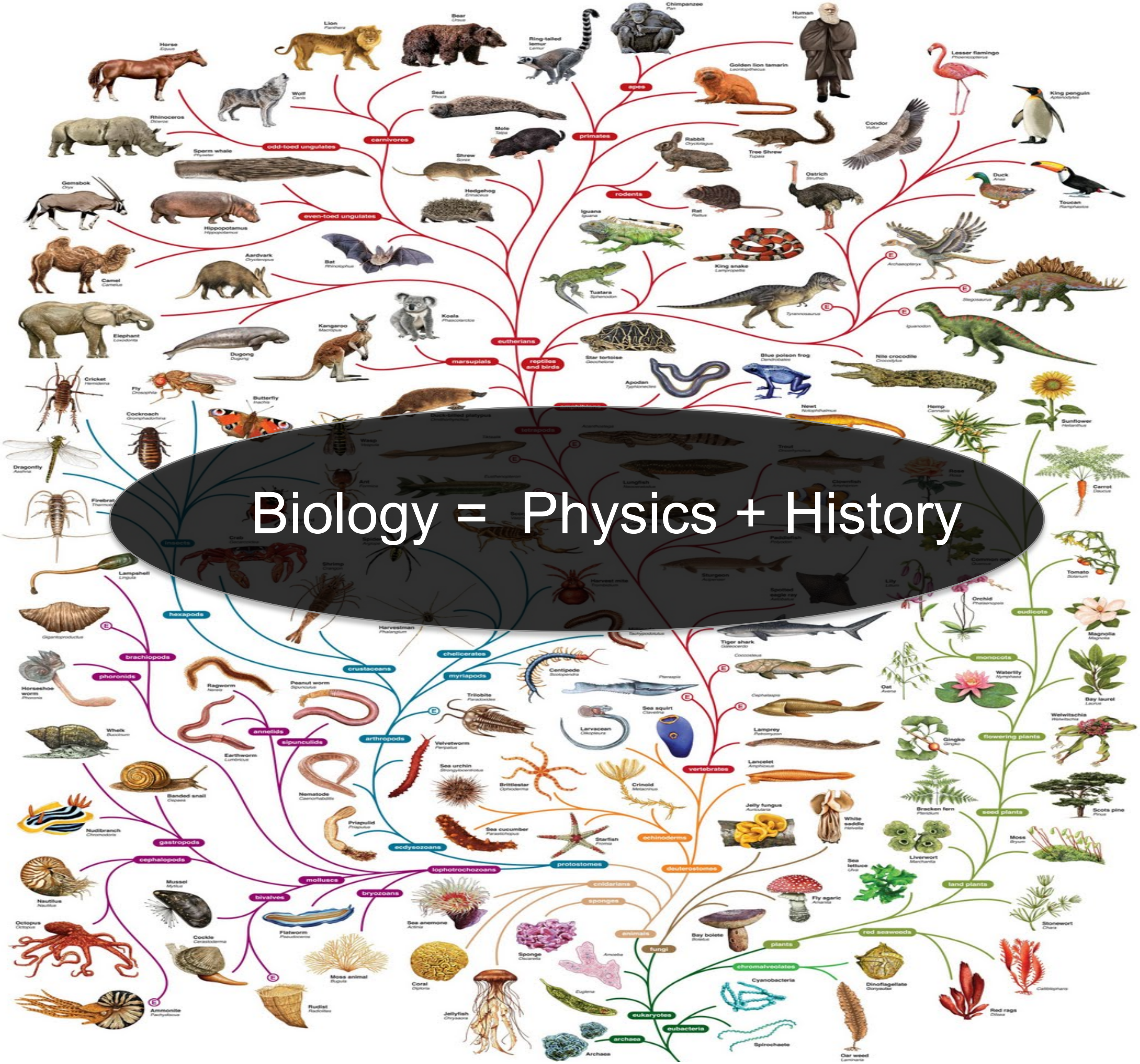
“ The only thing more unreasonable than the effectiveness of mathematics in physics is its ineffectiveness in biology. ”

Israel Gelfand

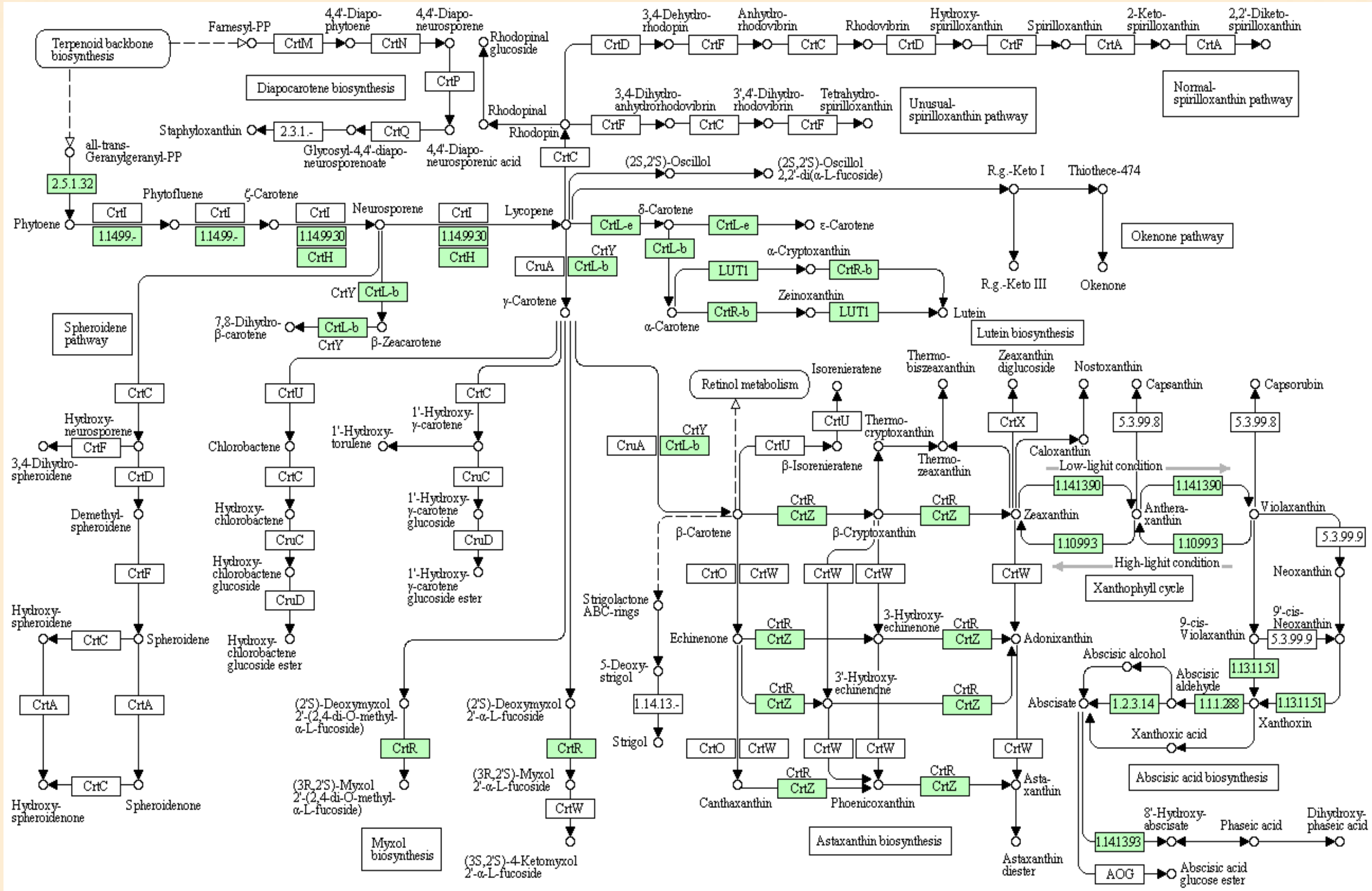
“ … unreasonable effectiveness of mathematics in the natural sciences ”

Eugene Wigner

Why is biology different ?



Biology = Physics + History



Historical document

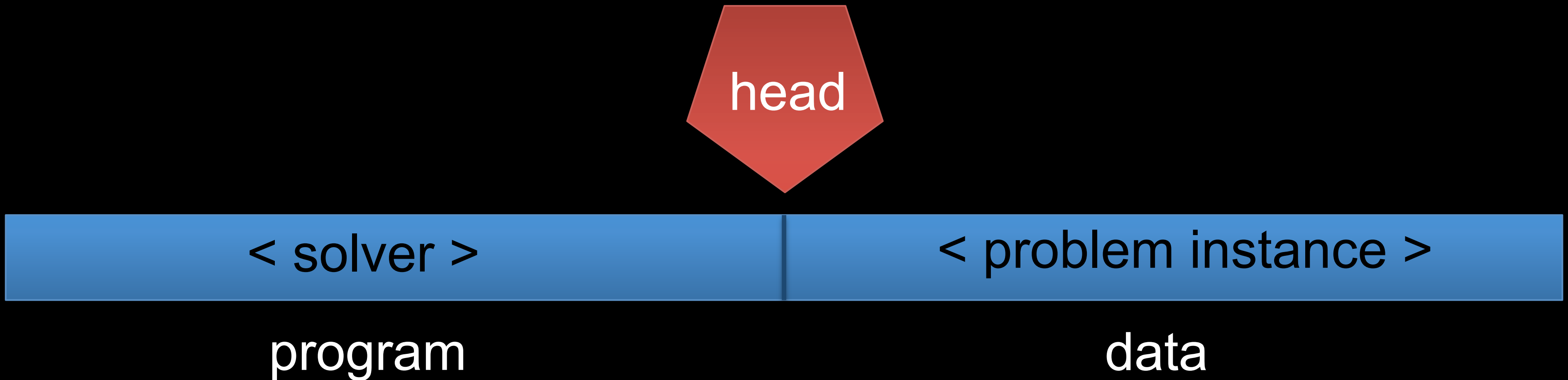
History may repeat itself…

but not quite enough for mathematics

Mathematics = language of symmetry

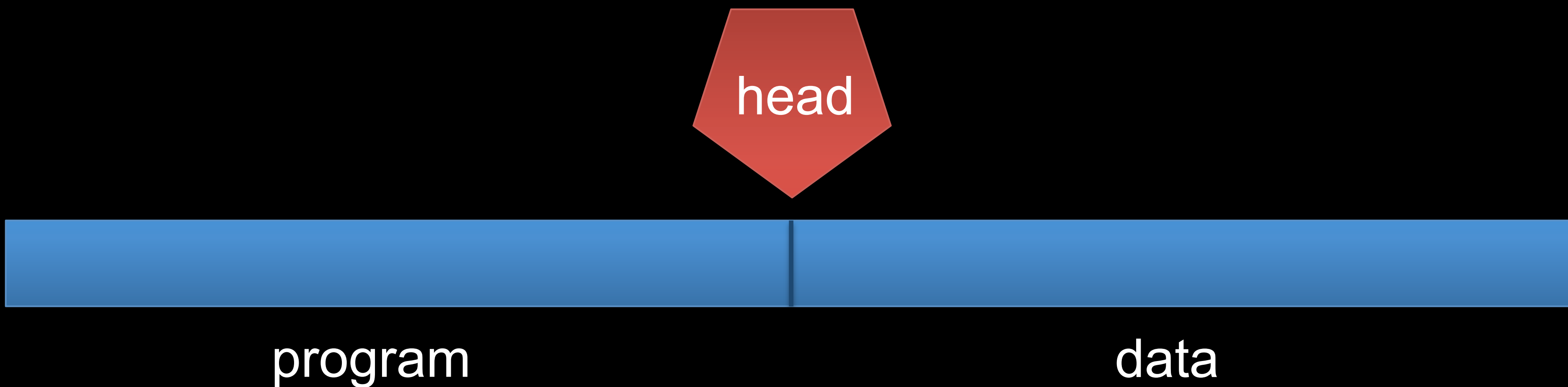
Algorithms = language of memory

Universal Turing machine



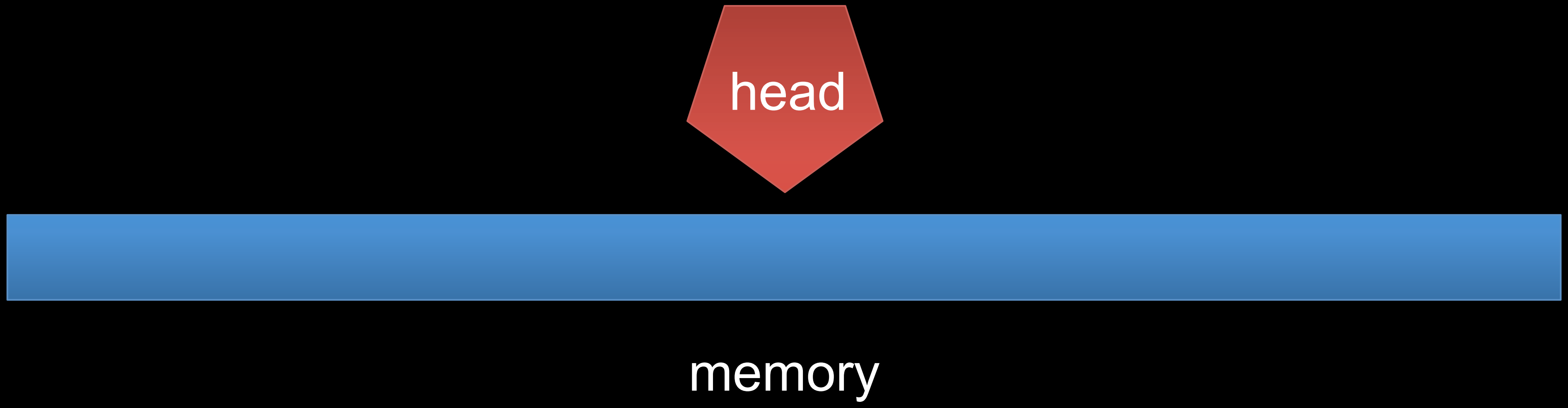
The distinction is not intrinsic to computation

Universal Turing machine

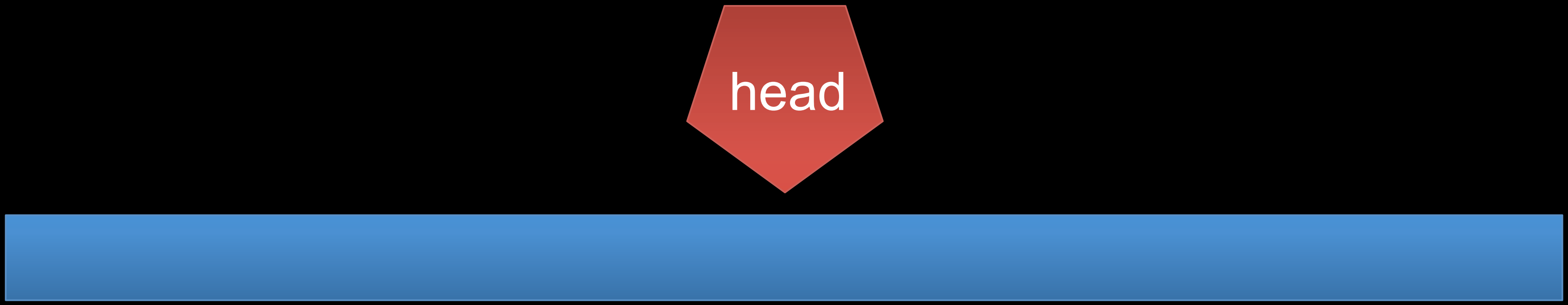


defined as the data that tends not to change

Universal Turing machine



In biology



memory works on many timescales

In biology

head

ribosomal dna … gene expression … dna binding

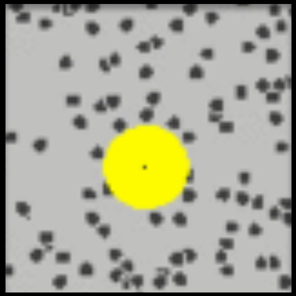
millions of years minutes microseconds

and length scales of ratio $\approx 1{,}000{,}000{,}000{,}000$

Scaling

Brownian motion

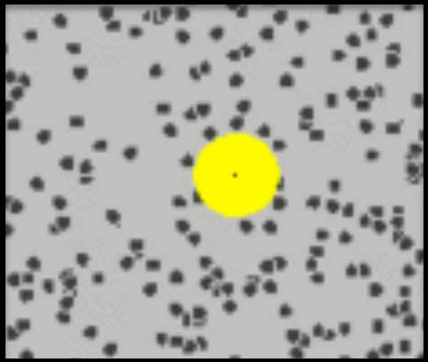
Microscopic



Intractable !

Deterministic Newtonian mechanics

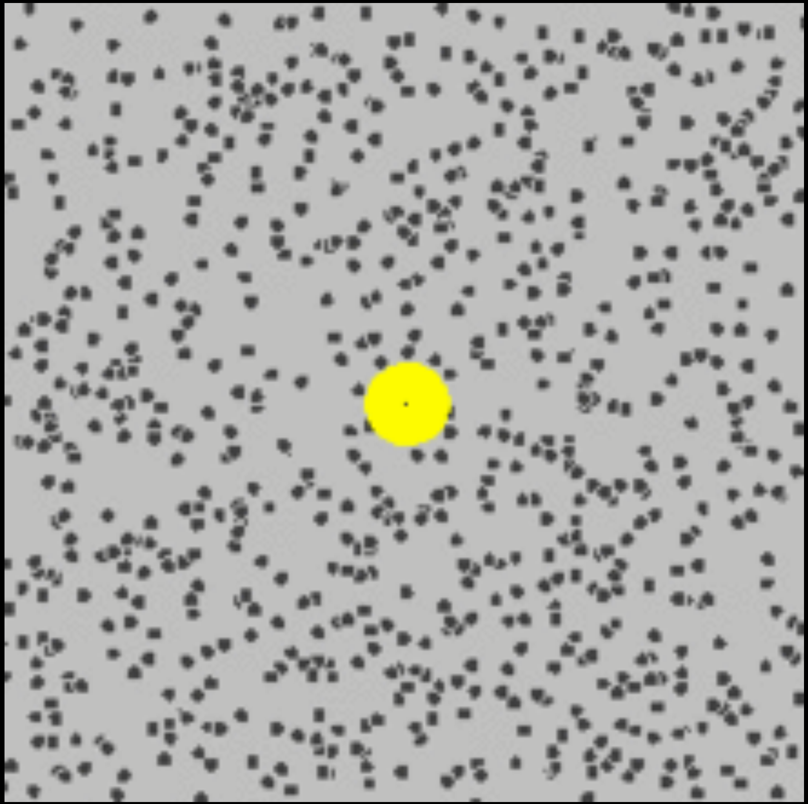
Mesoscopic



Scale-free !

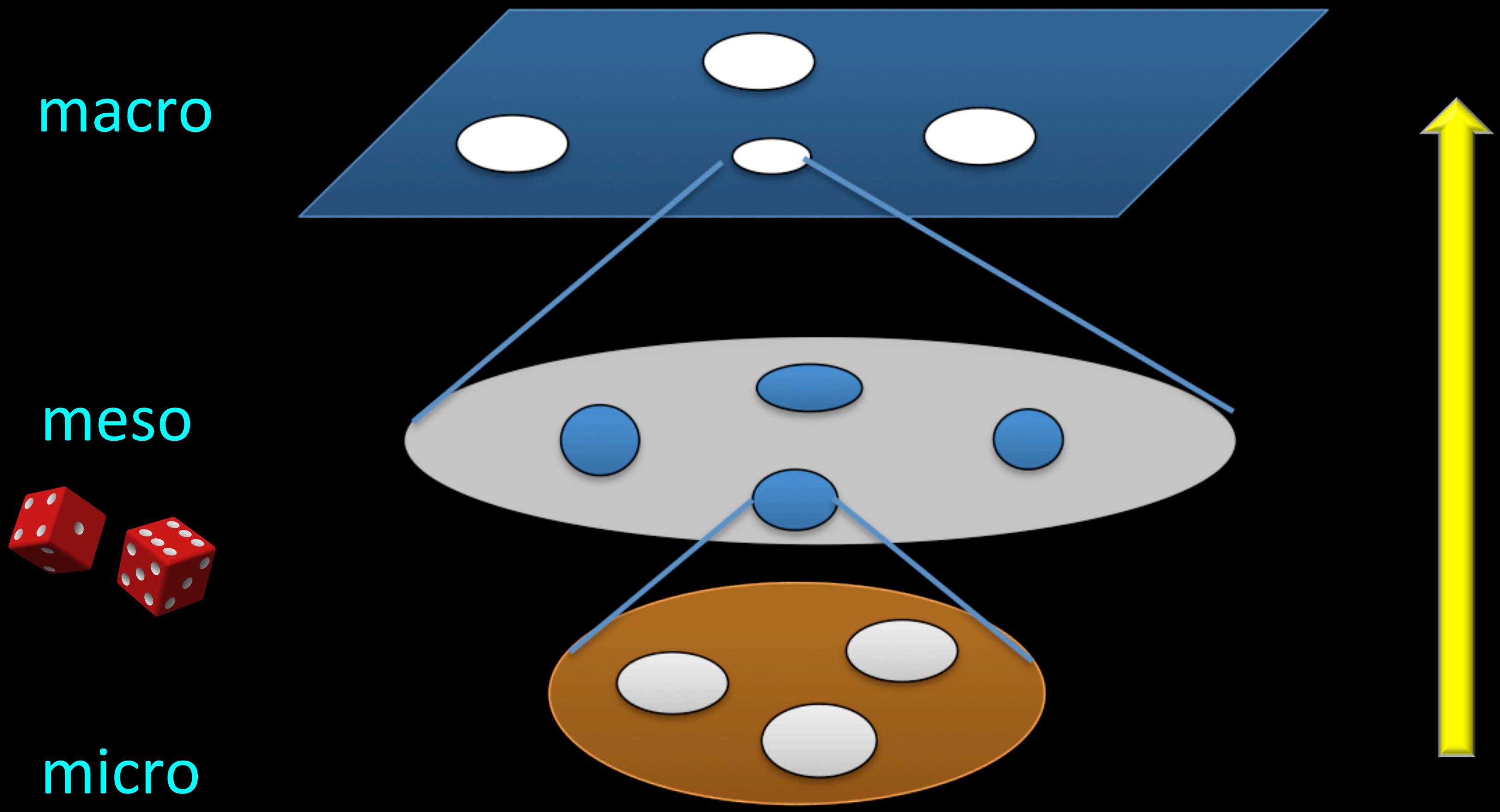
Stochastic Brownian motion

Macroscopic

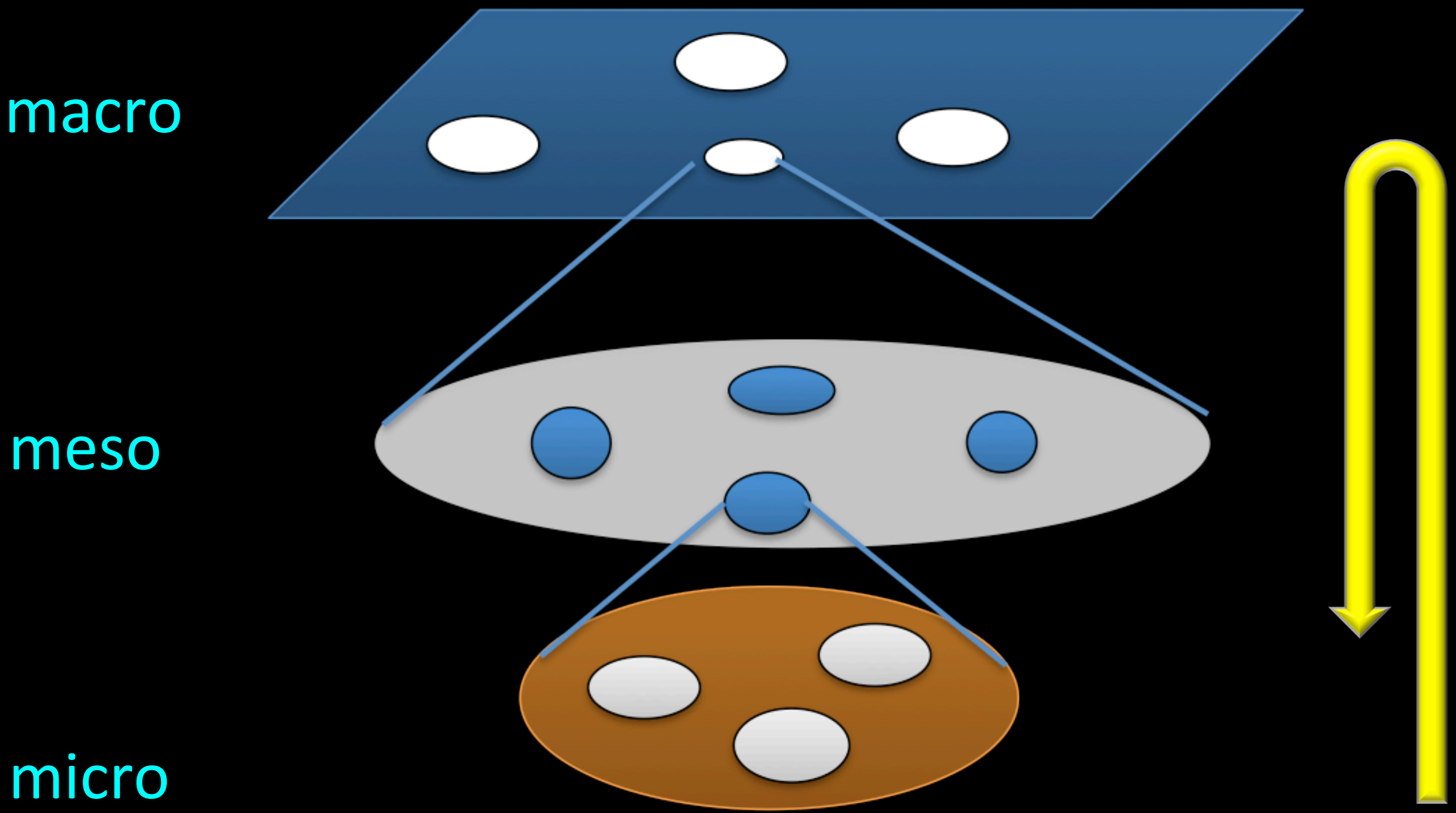


solvable

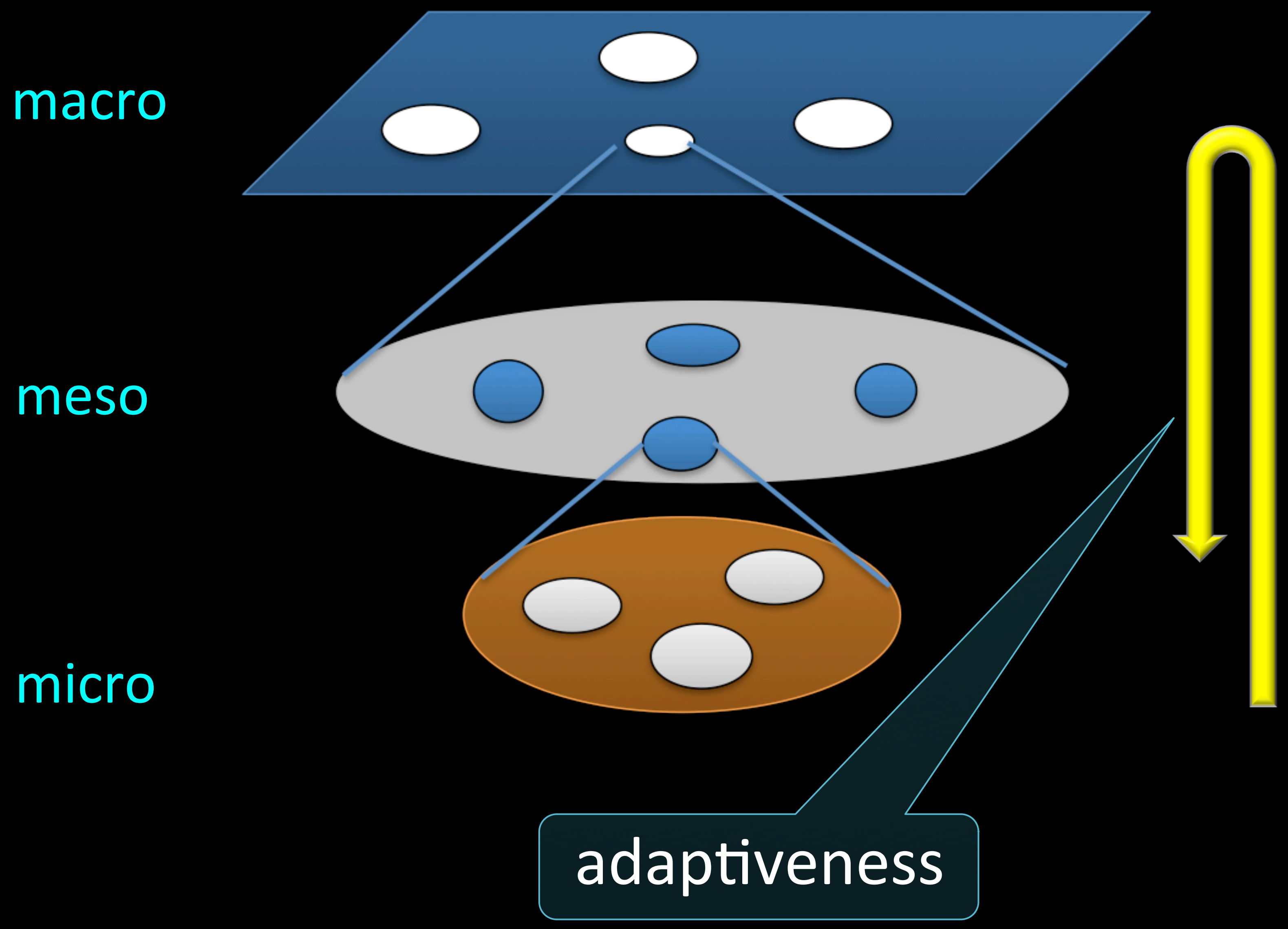
Deterministic diffusion



Causation in physics

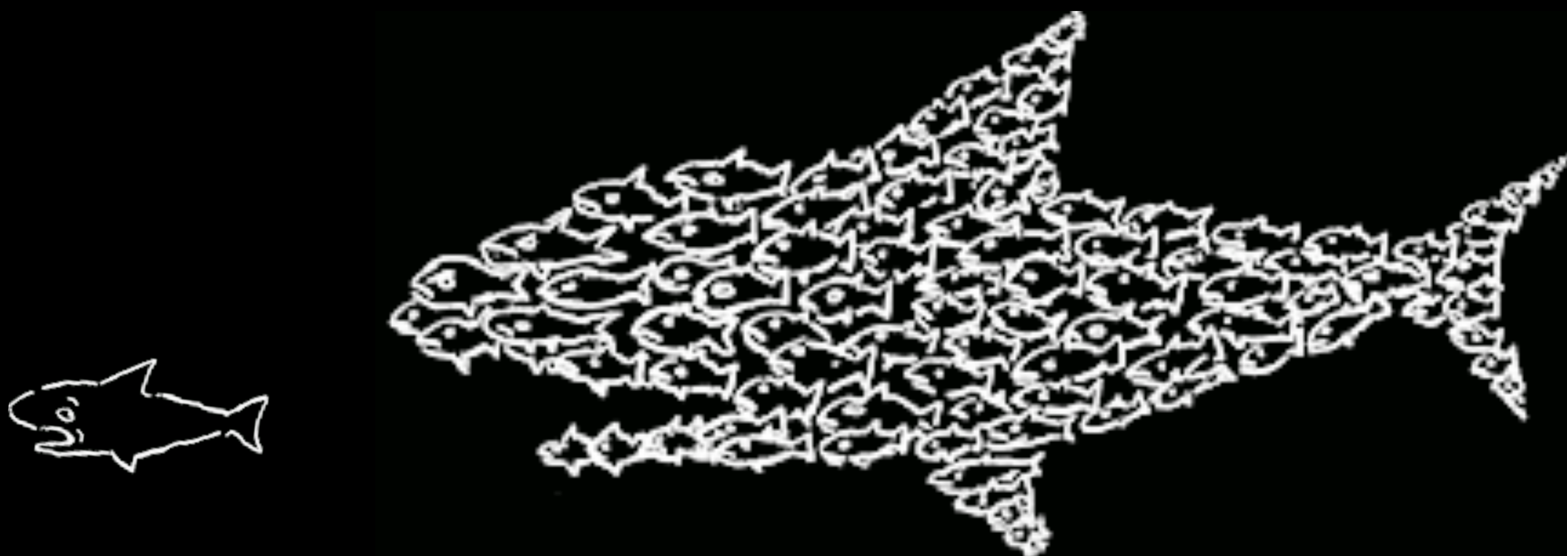


Causation in biology


macro
meso
micro
adaptiveness

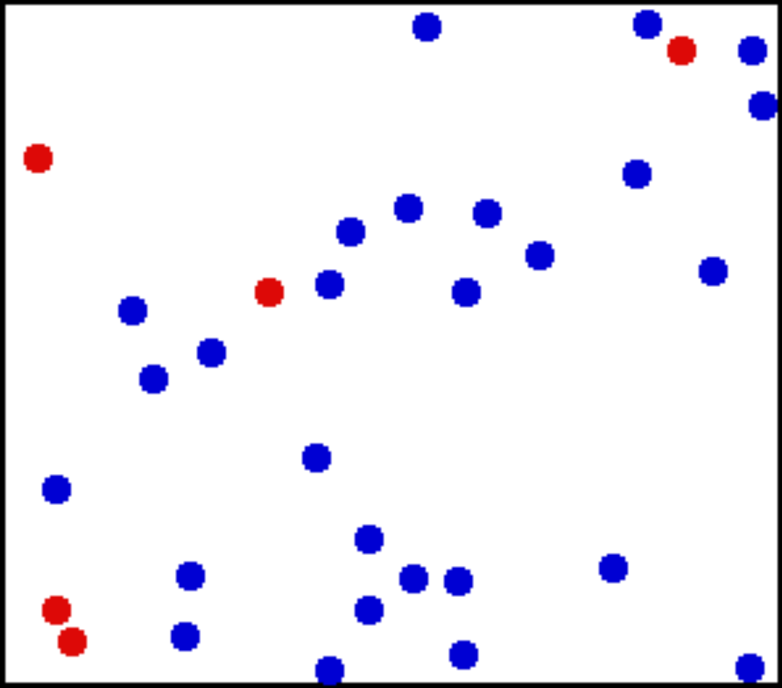
Nov. 1, 2

THE NEW YORKER

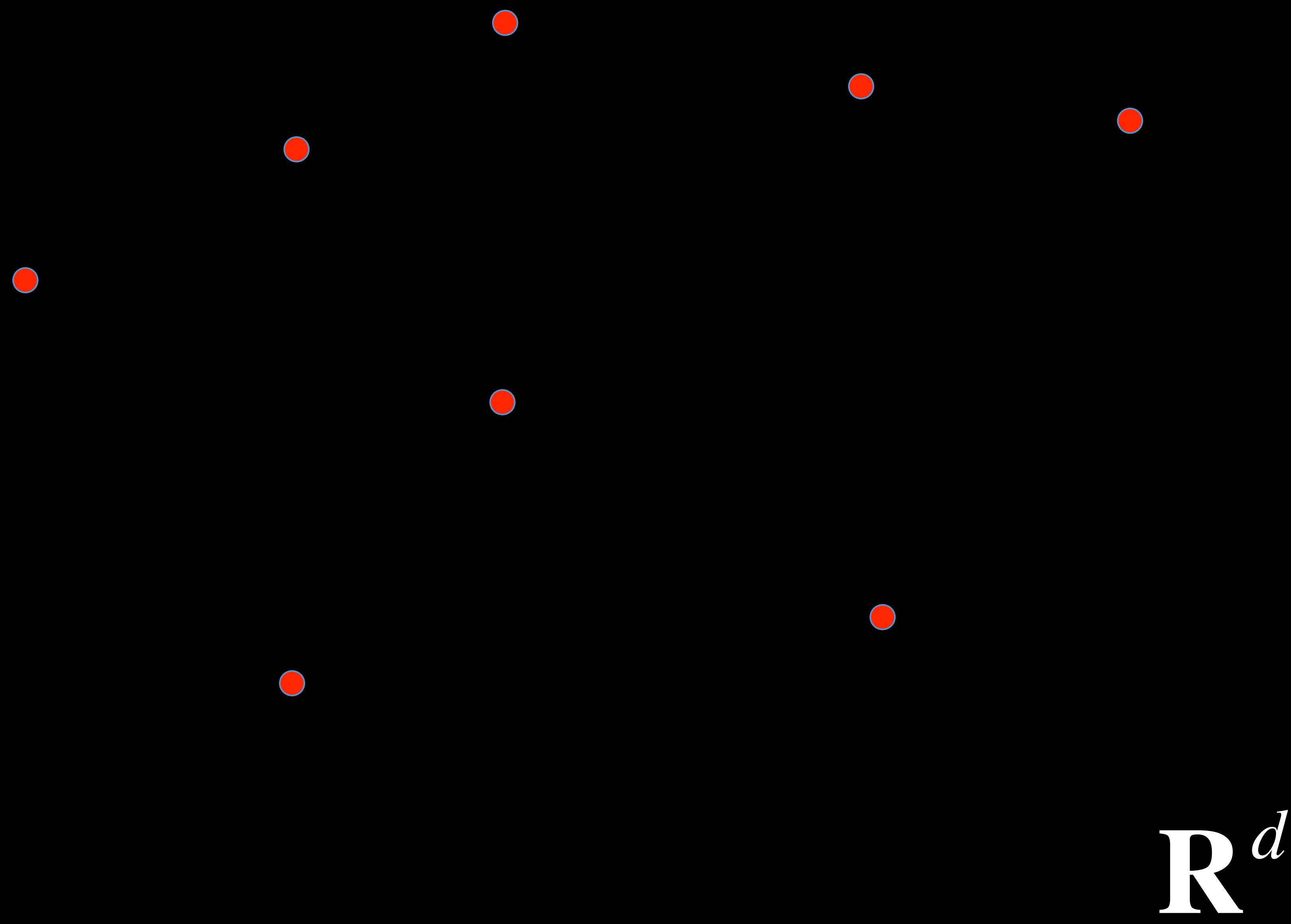


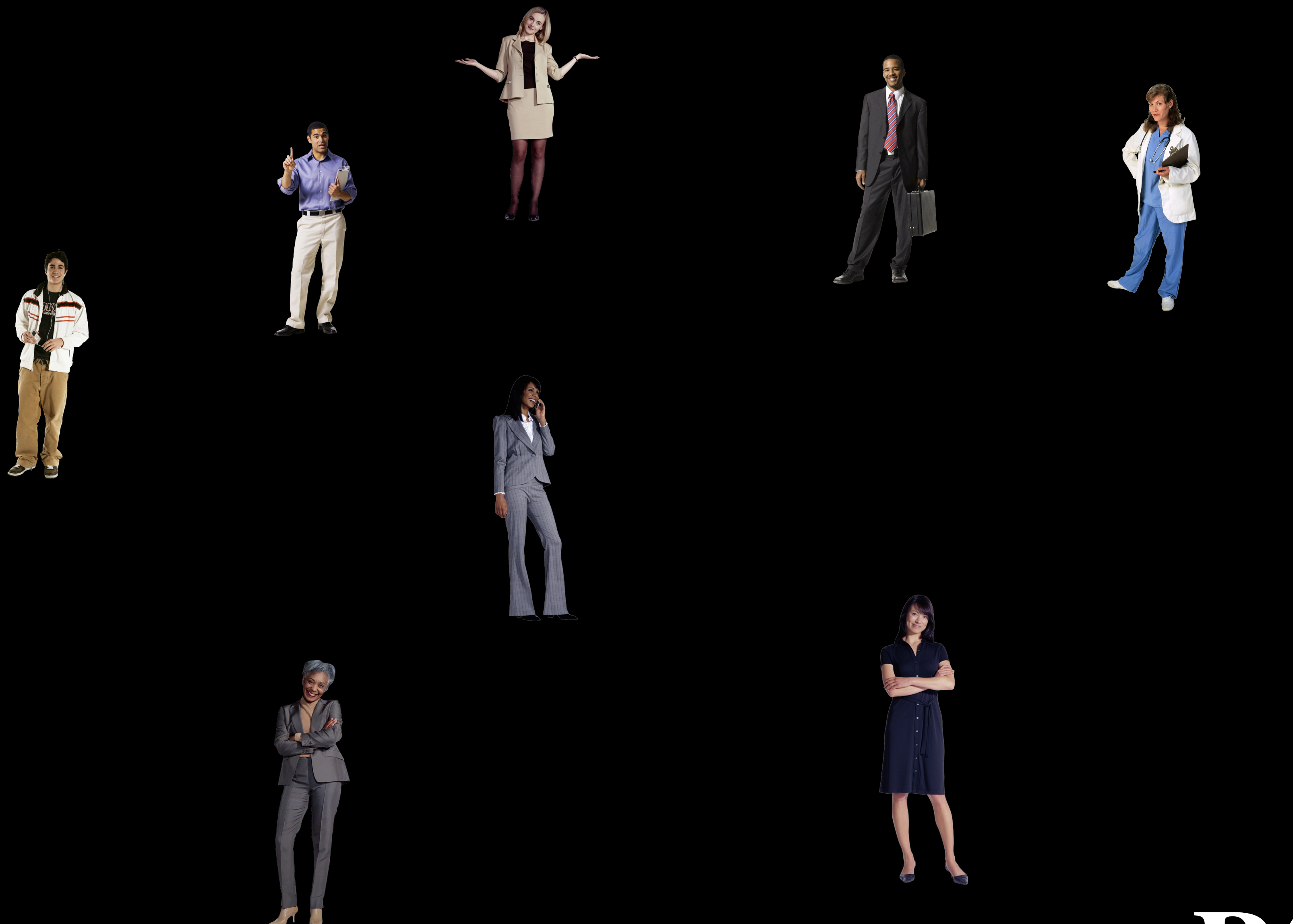
A model to study mixed scales

Influence systems

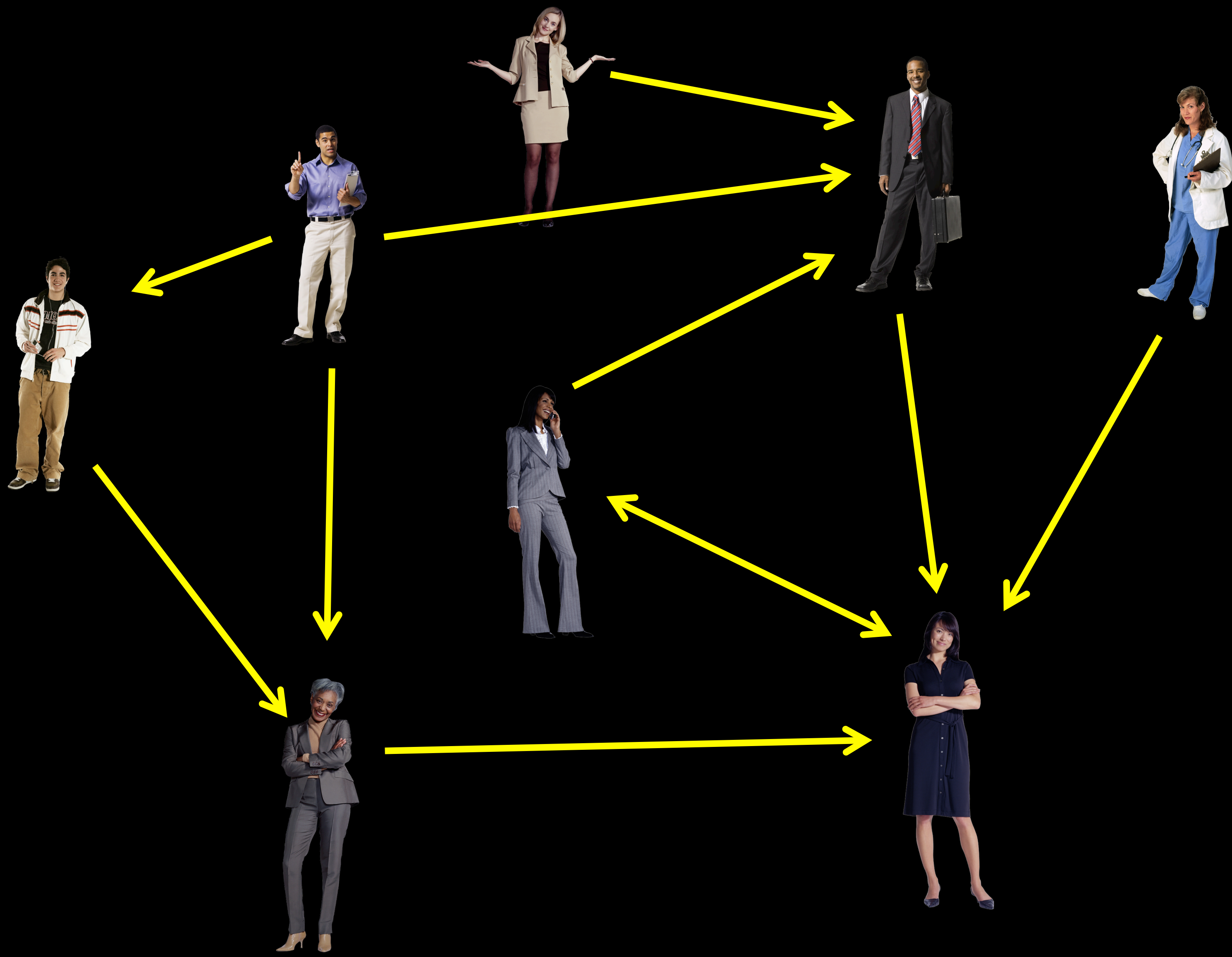


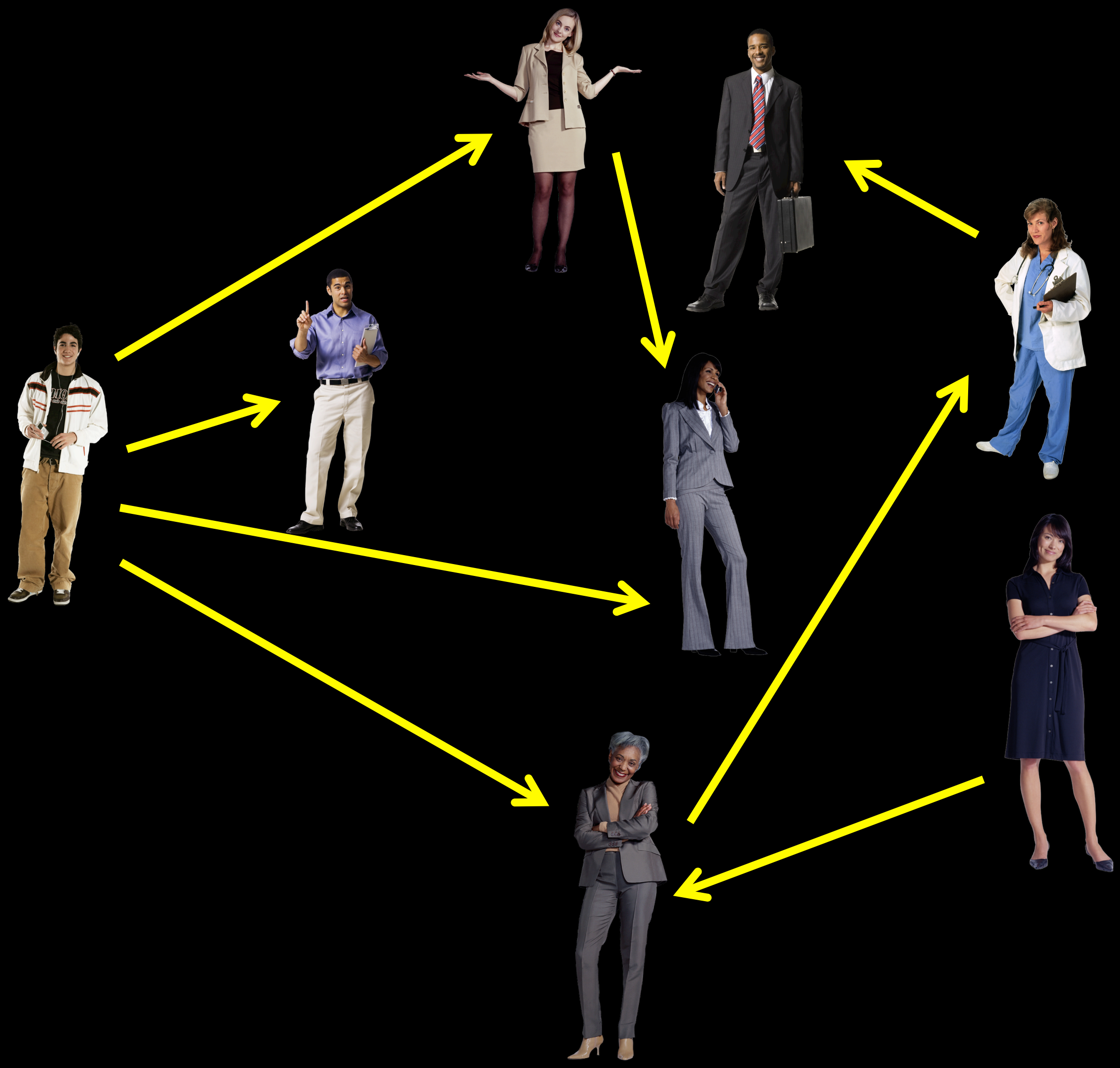
Interacting particles, each one with its own physical law !

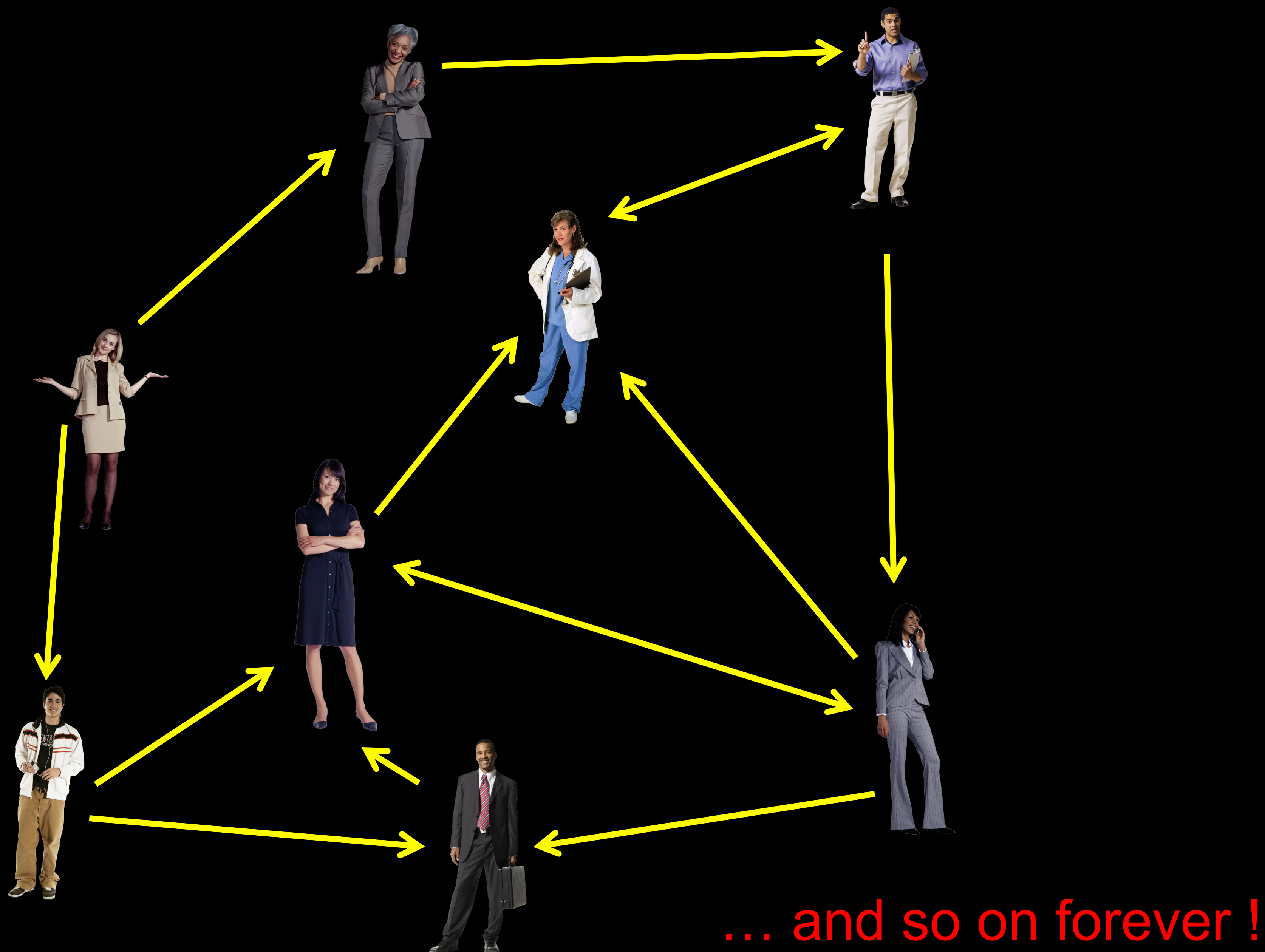

$\mathbf{R}^d$



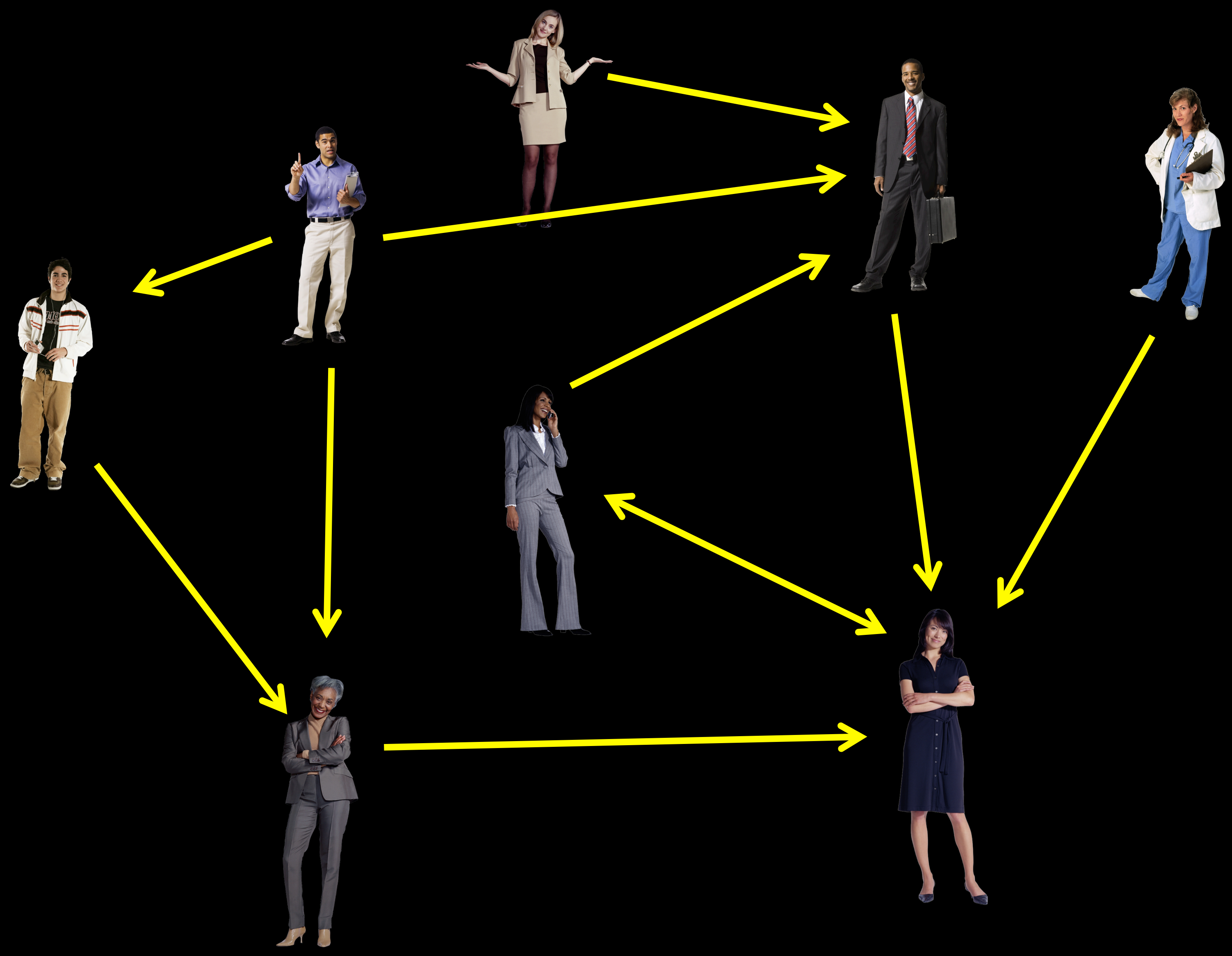
$\mathbf{R}^d$



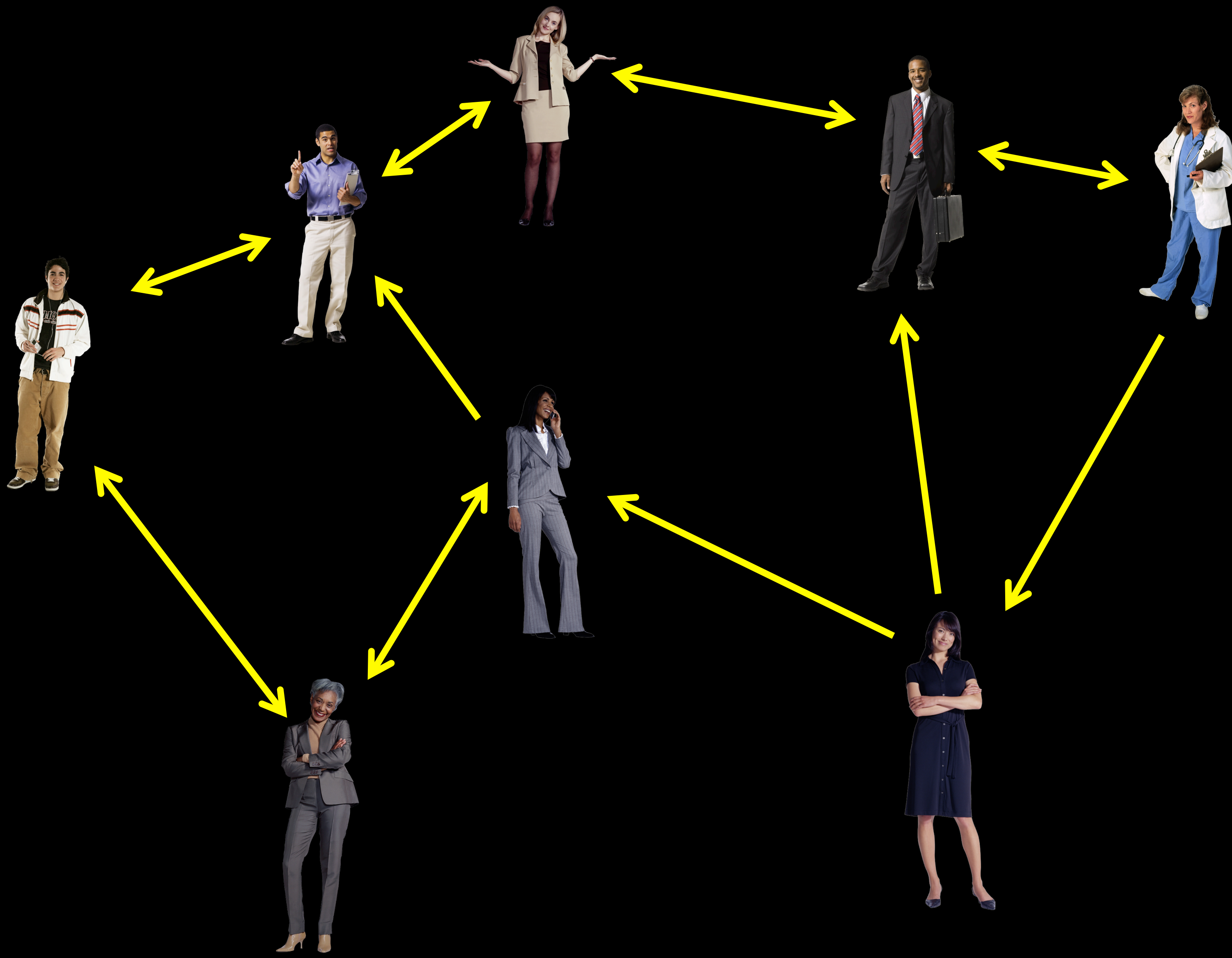



… and so on forever !

How are the networks formed ?



network = *f* (agents' positions)

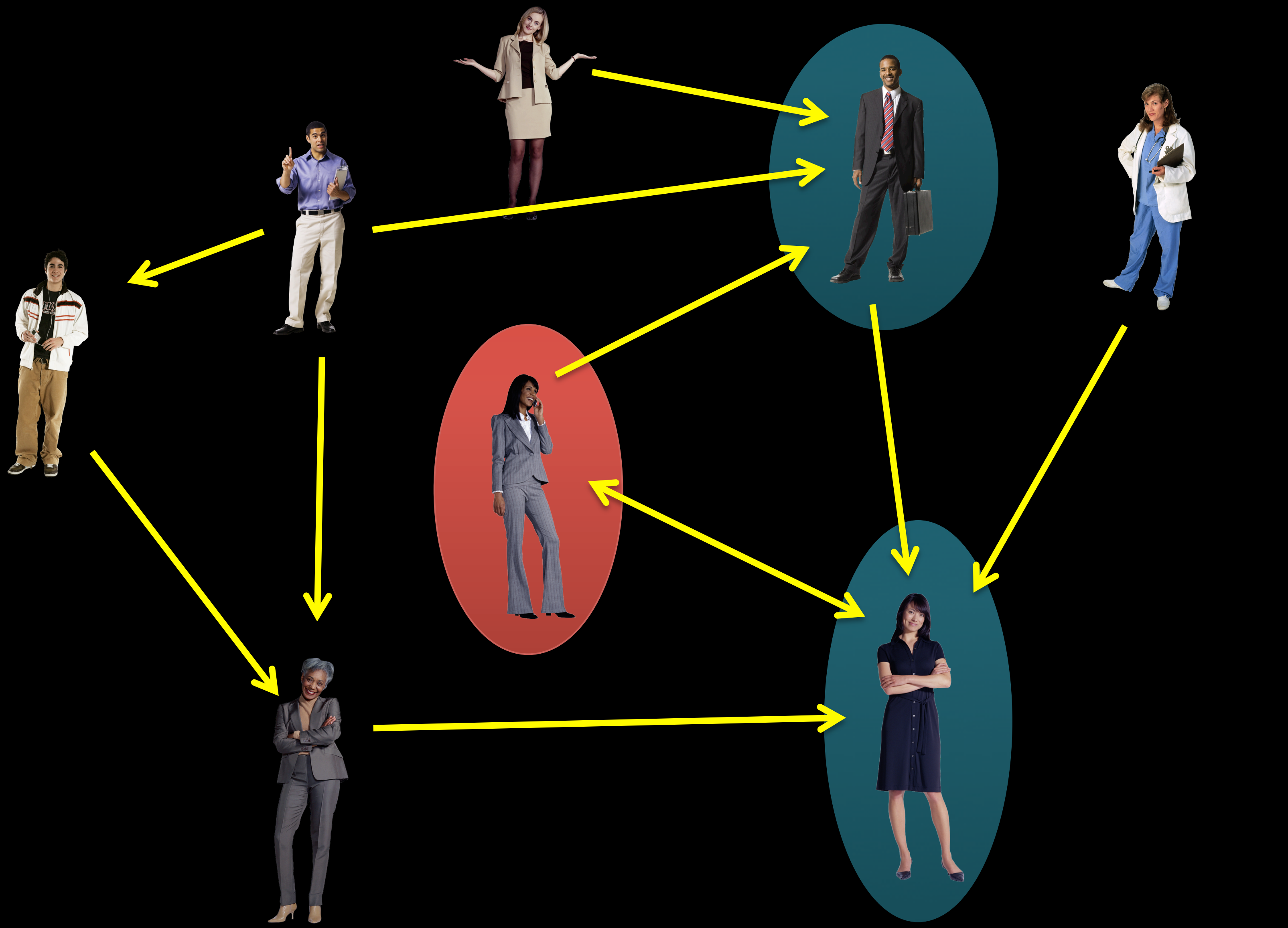


for example... two nearest neighbors

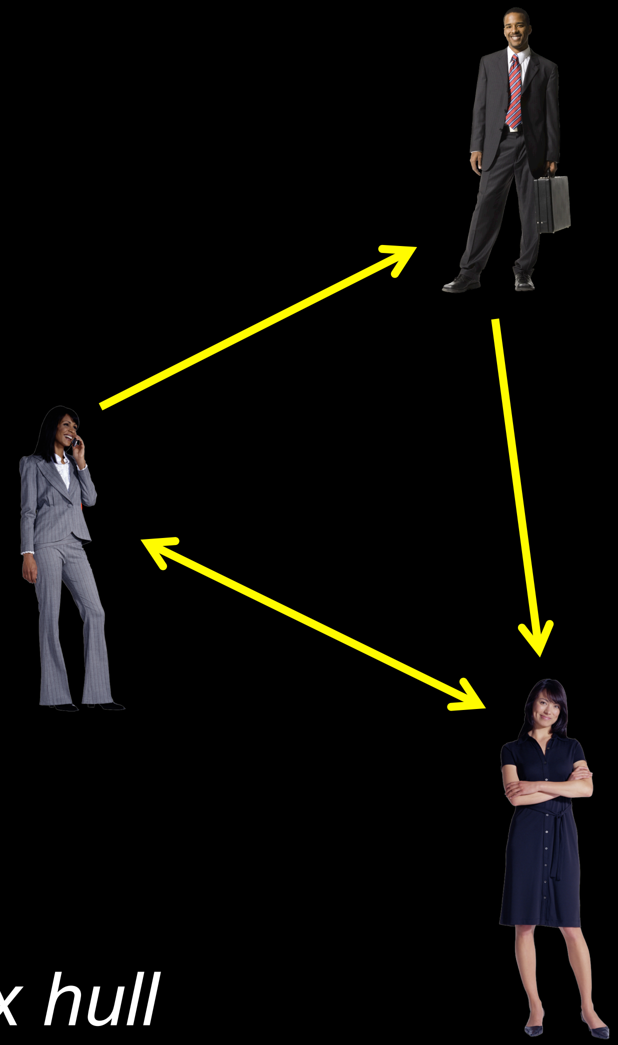
Any first-order sentence over reals is OK

$$\forall y_1 \, \exists y_2 \, \forall y_3 \cdots P(\text{agent locations}, y_1, y_2, \ldots) \geq 0$$

How do the agents move?

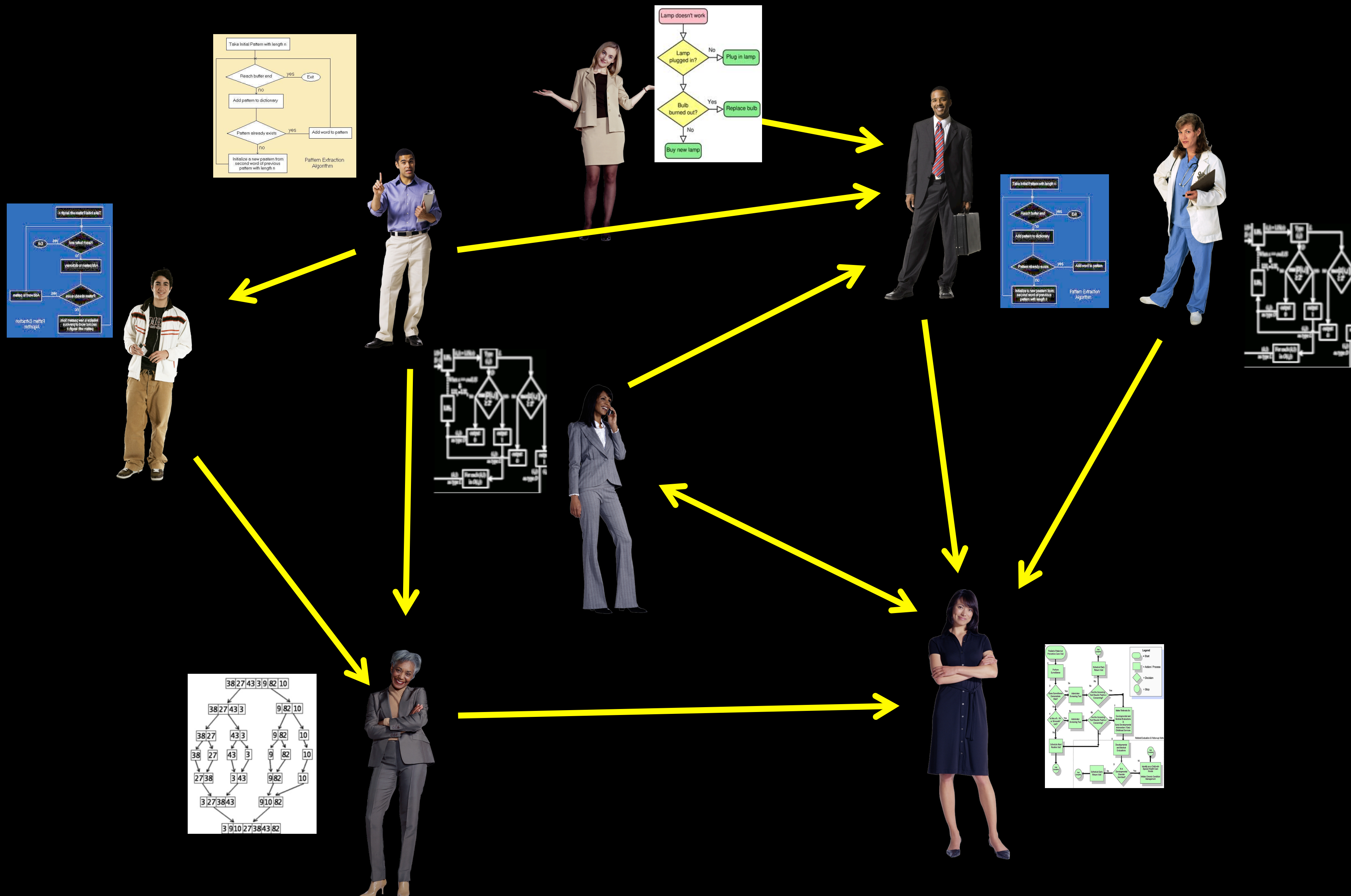


Her next position is function only of her neighbors & herself



If she stays in convex hull

the system is called diffusive



Each agent has its own interaction & motion algorithm

Its dis/coordinated function & memory

To specify a diffusive influence system...

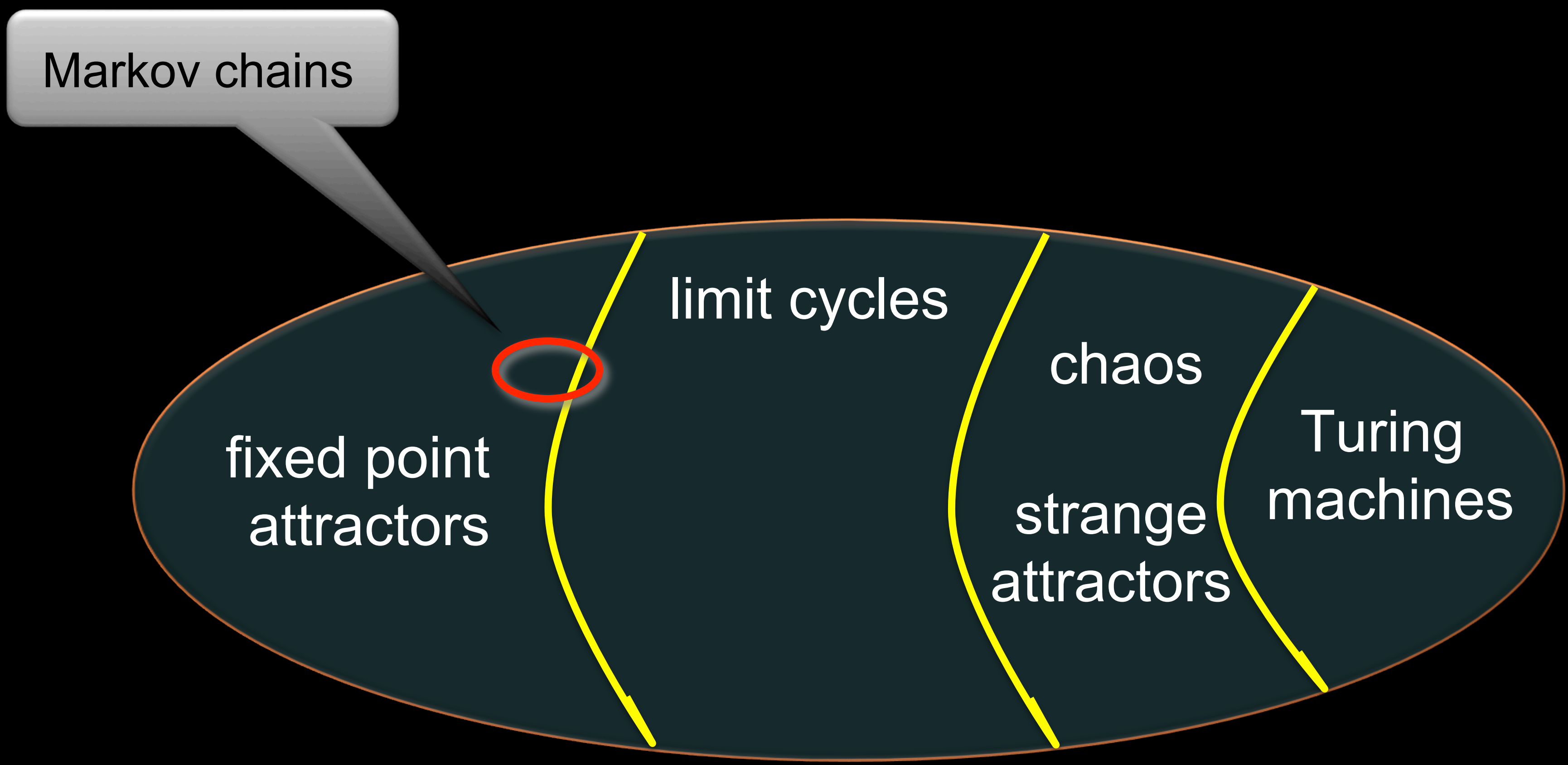
- a set of formulas

$$\forall y_1 \, \exists y_2 \, \forall y_3 \cdots P\,(\text{agent locations}, y_1, y_2, \ldots) \geq 0$$

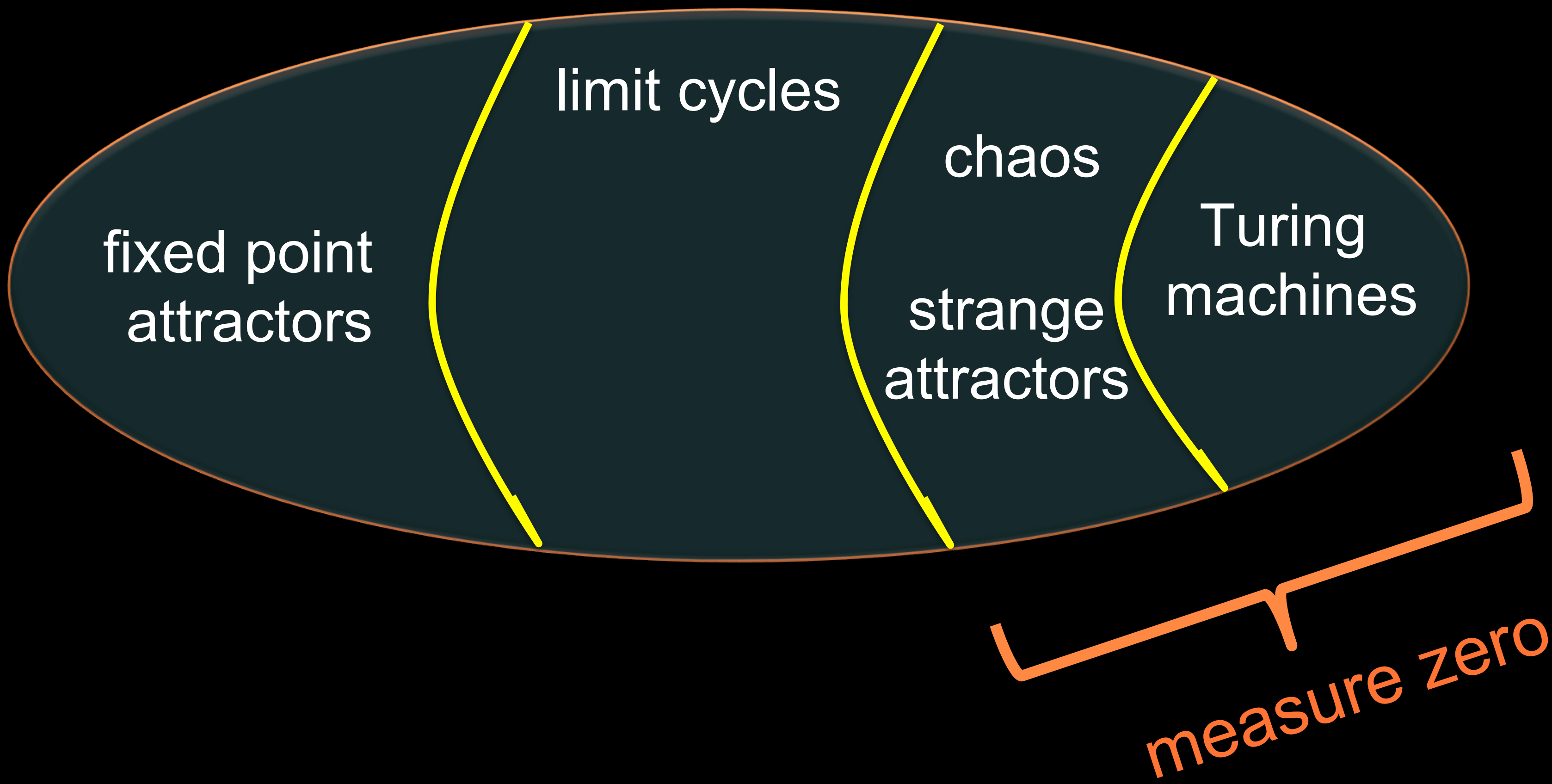
- a set of stochastic matrices

Space of diffusive influence systems

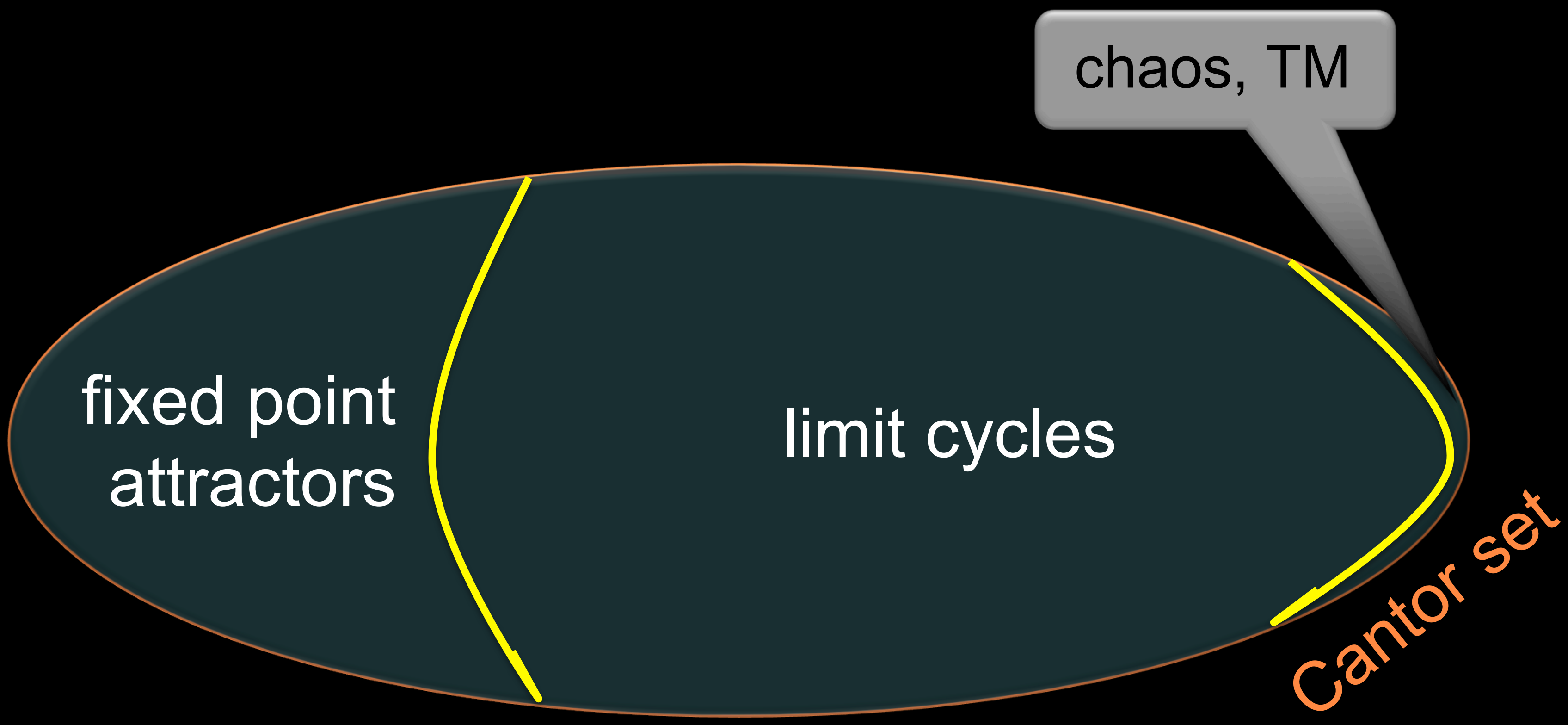
A very rich theory


Markov chains
limit cycles
chaos
Turing machines
fixed point attractors
strange attractors

Theorem [C ’12]


fixed point attractors
limit cycles
chaos
strange attractors
Turing machines
measure zero

Very surprising: all Lyapunov exponents are ≤ 0 !!!



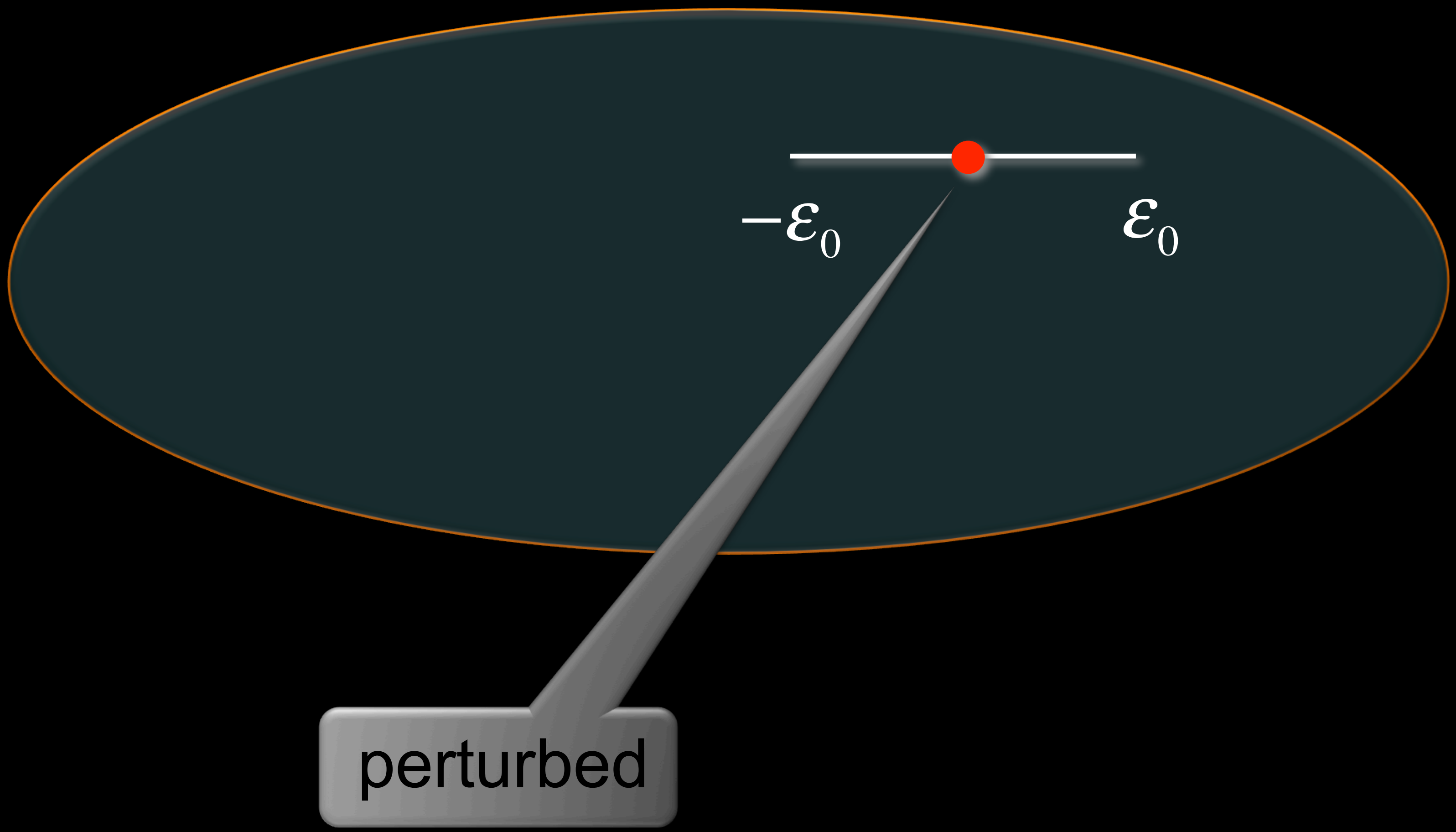
To perturb a diffusive influence system...

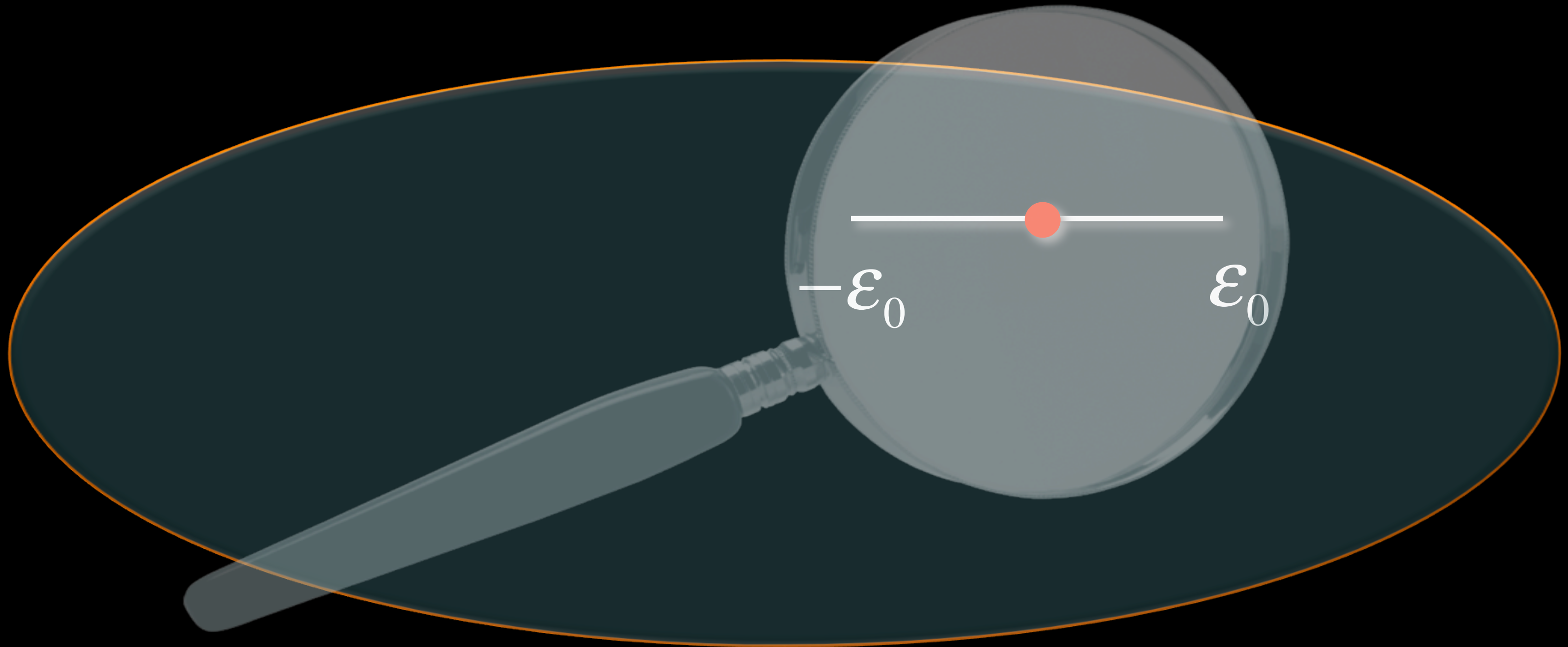
- a set of formulas

$$\forall y_1 \, \exists y_2 \, \forall y_3 \cdots P(\text{agent locations}, y_1, y_2, \ldots) \geq \varepsilon$$

- a set of stochastic matrices

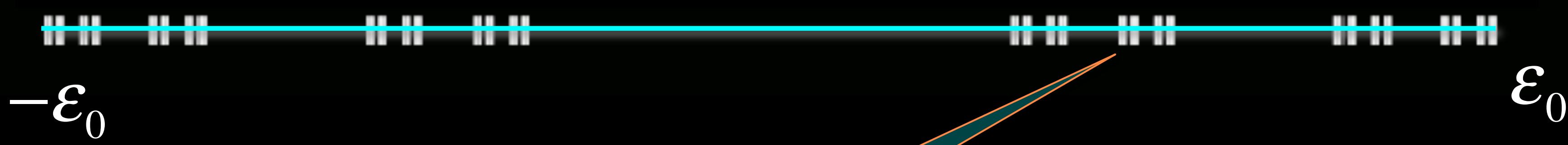
Set of diffusive influence systems





$-\varepsilon_0$
ε_0

Asymptotically periodic everywhere else

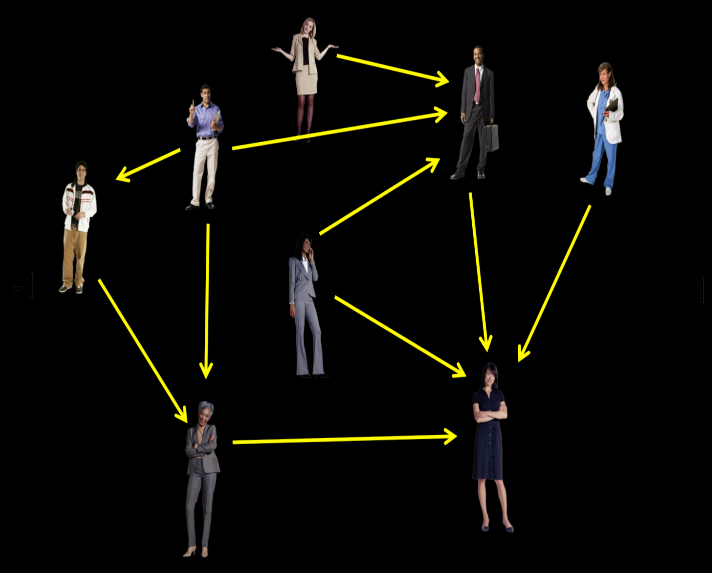


TM, chaotic systems

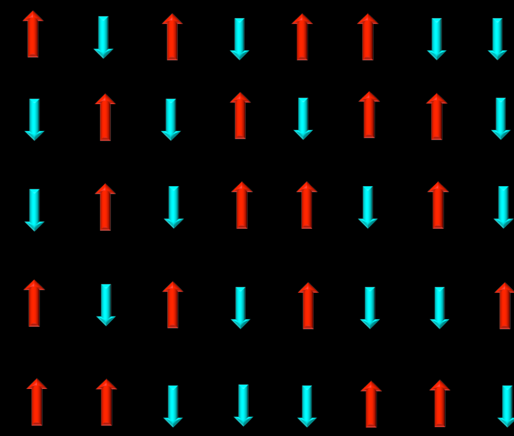
Dynamic renormalization

“ or how to analyze mixed scales ”

Influence system



Ising model



Agents keep interacting

entropy

Particles keep jiggling

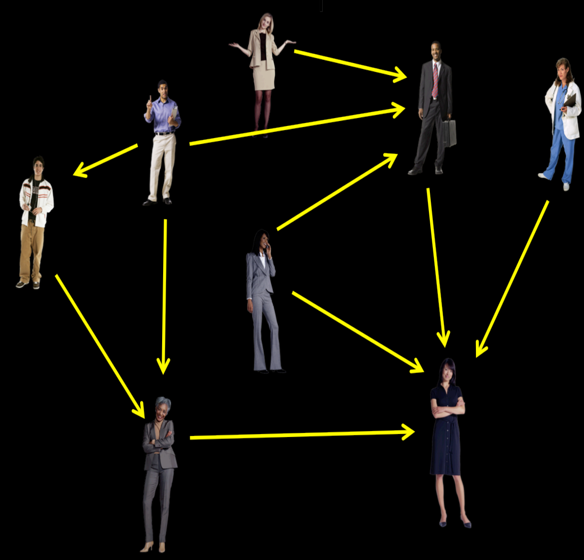
Criticality (2nd order phase transitions)

Agents want to move toward their neighbors

energy

Particles want to jiggle in sync with neighbors

Influence system

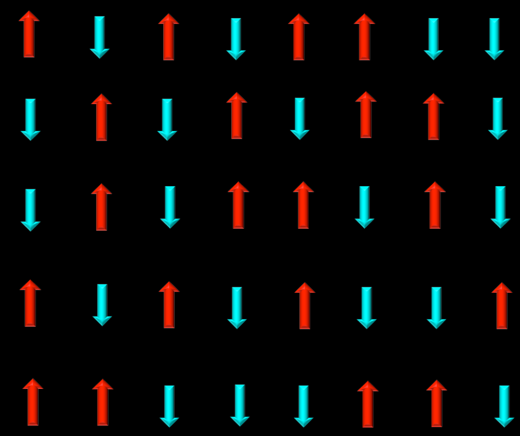


Topology changes endogenously

Infinite # of critical points

Out of equilibrium

Ising model

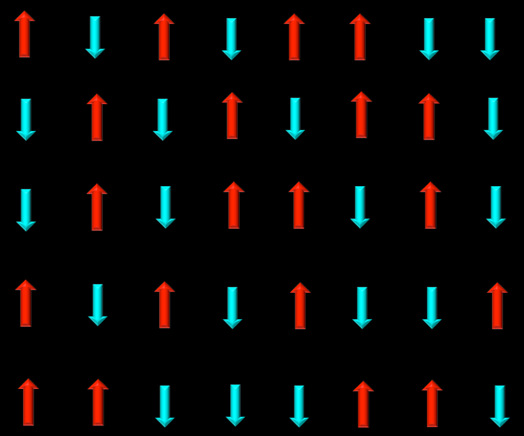


Topology is fixed

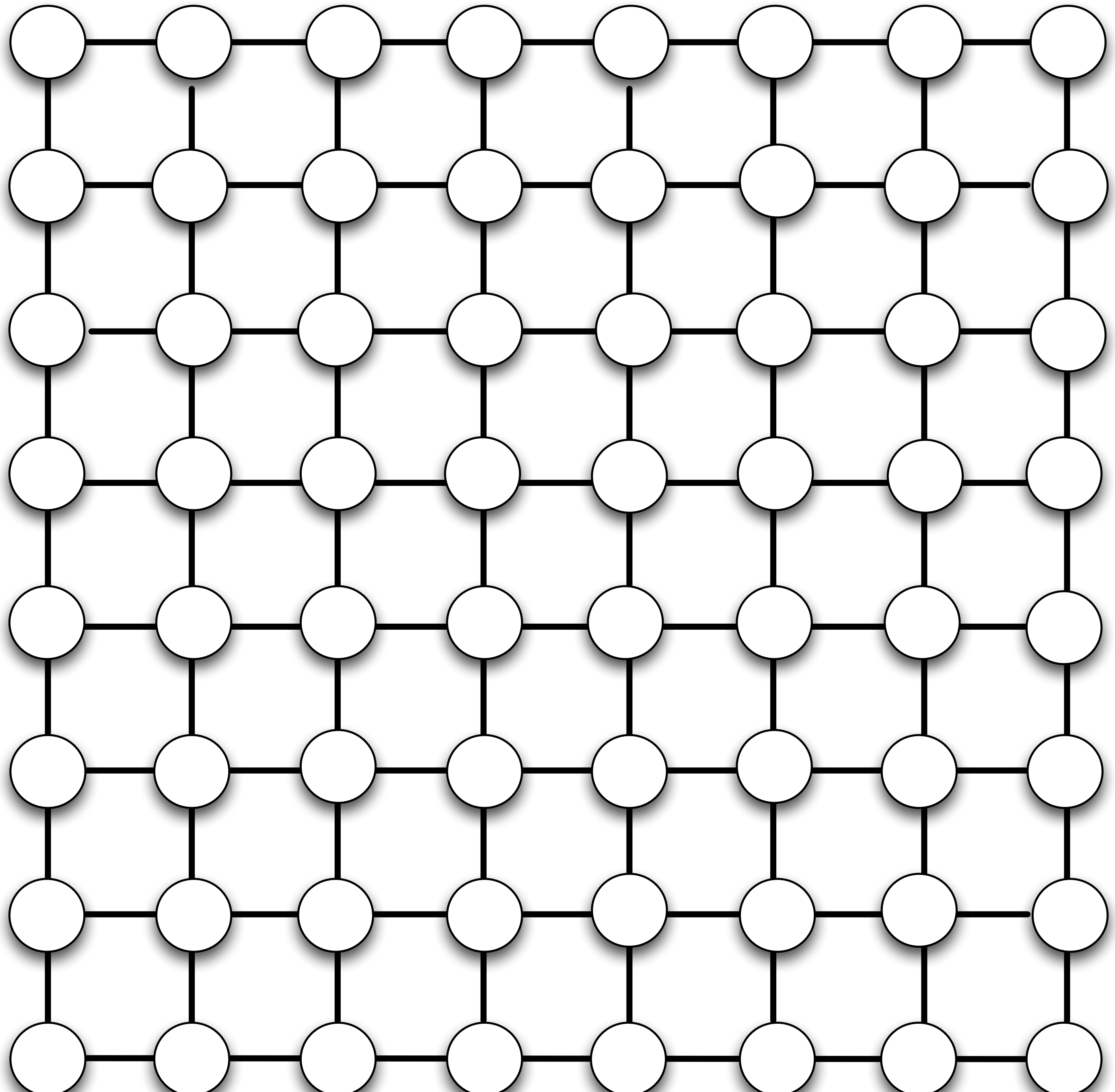
Single critical point

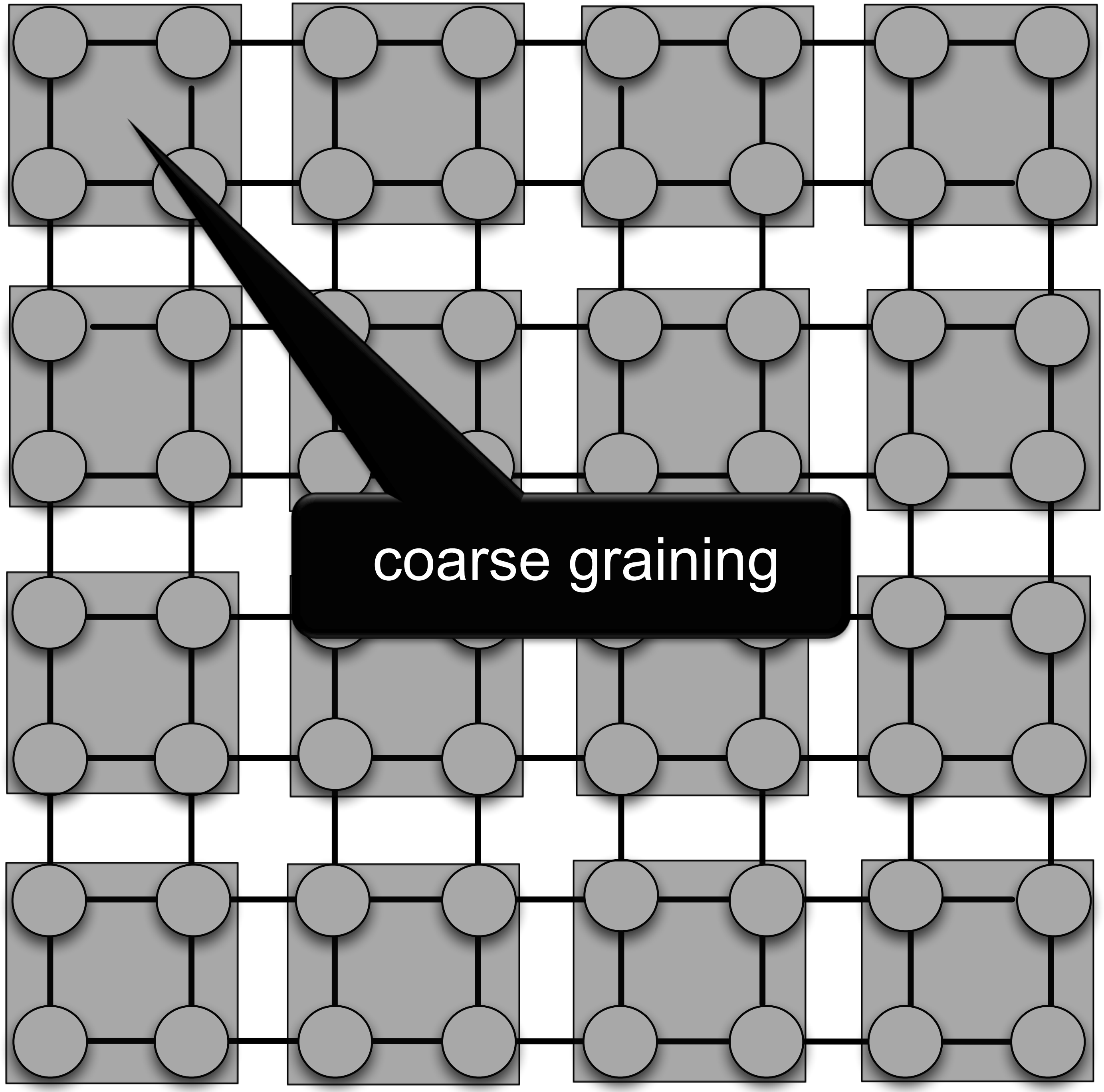
Equilibrated

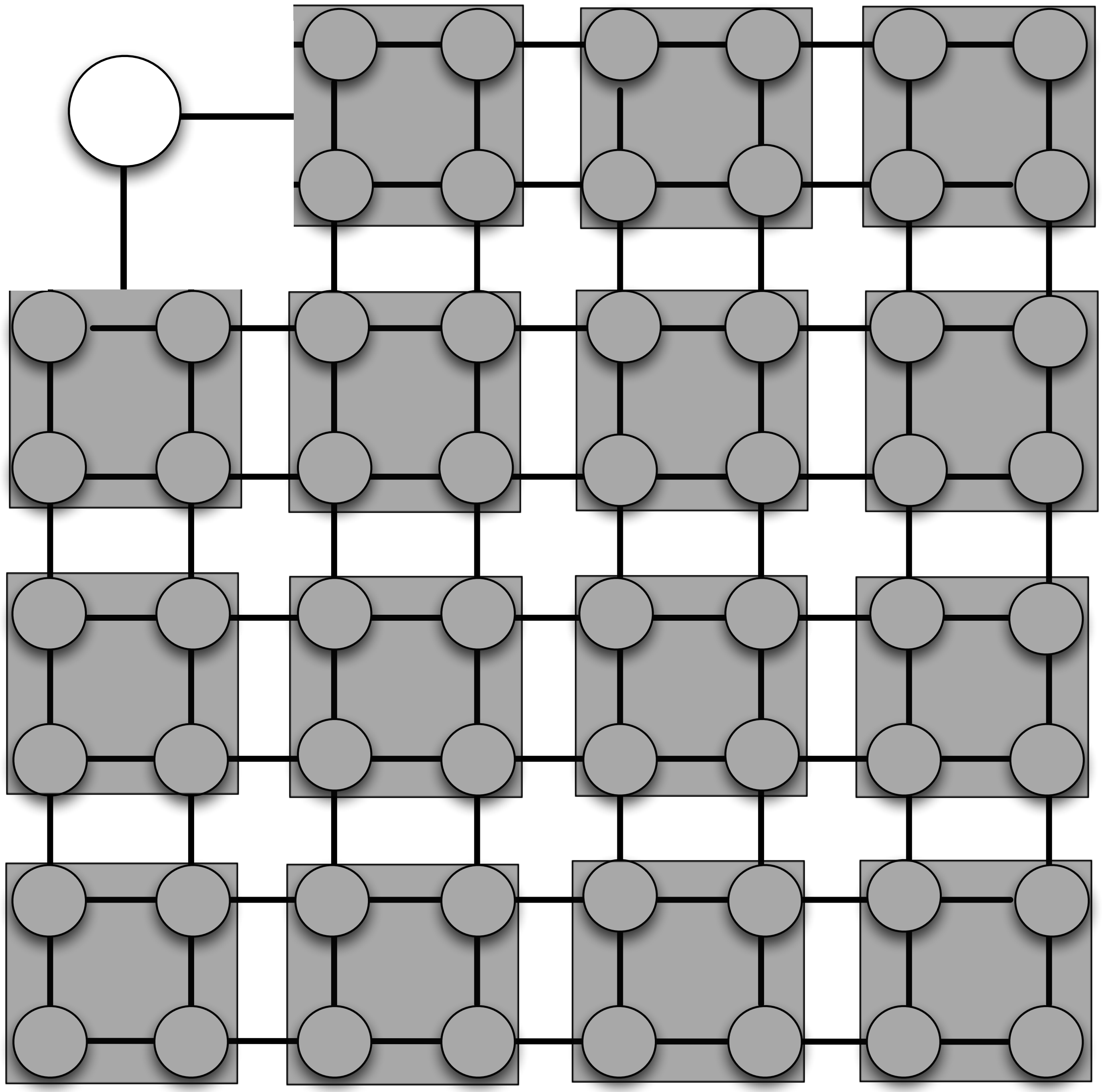
Ising model

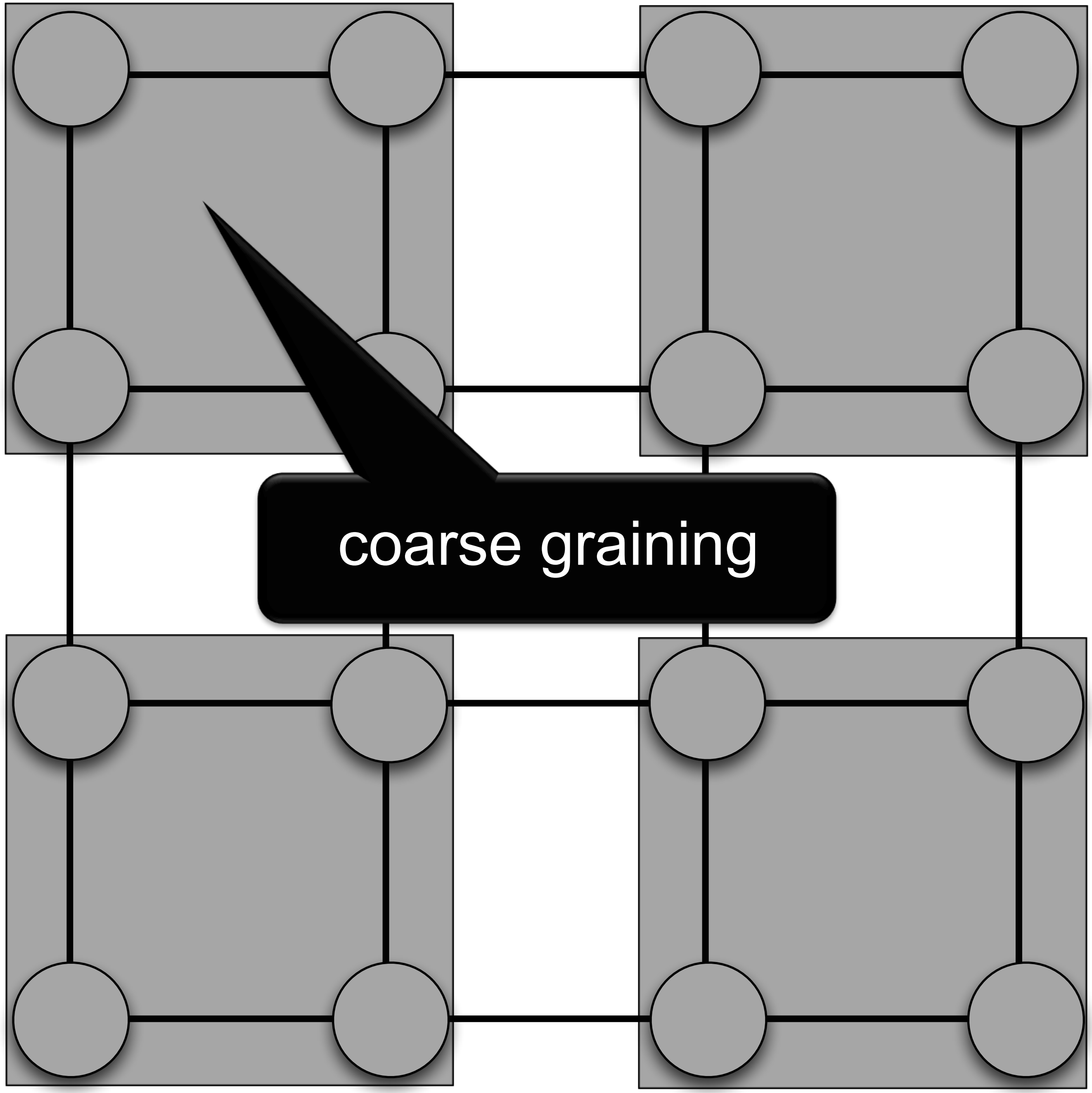


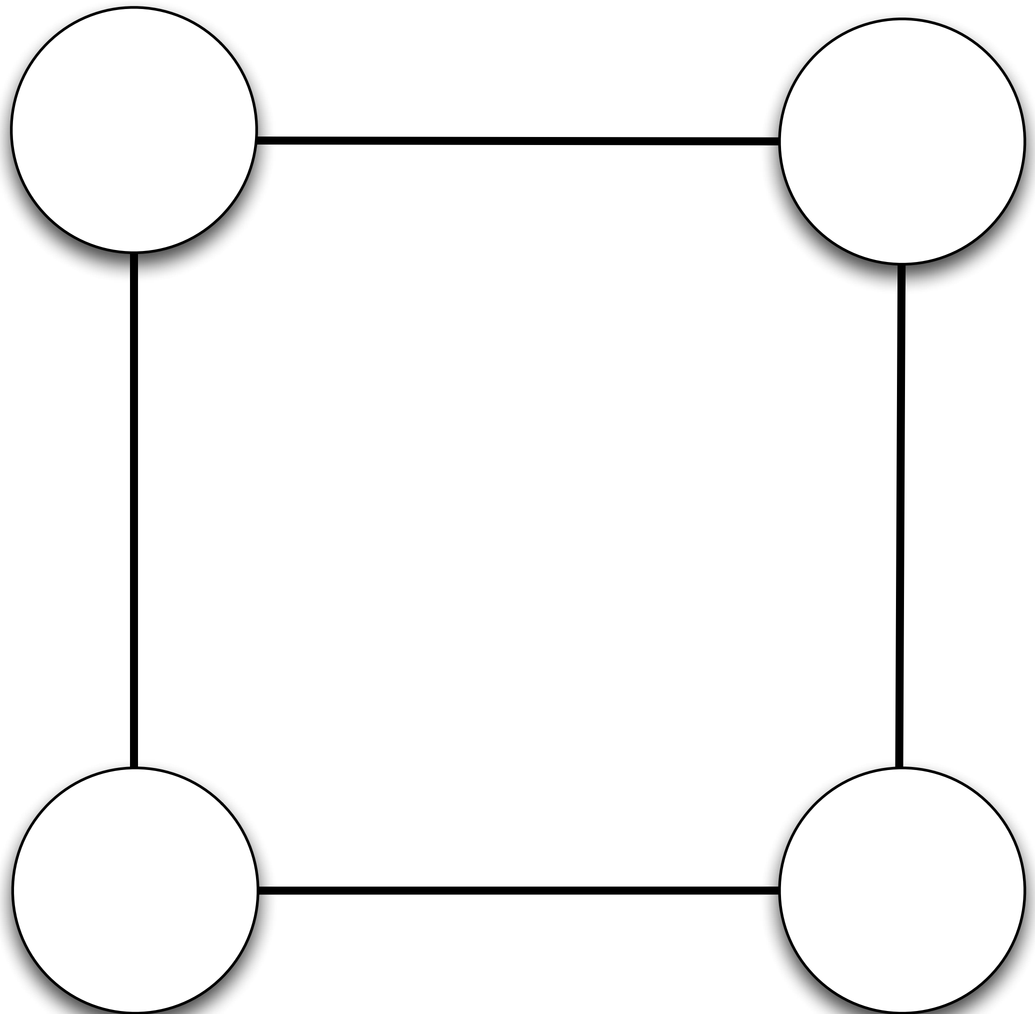
Renormalization group [Kadanoff, Wilson, …]




coarse graining

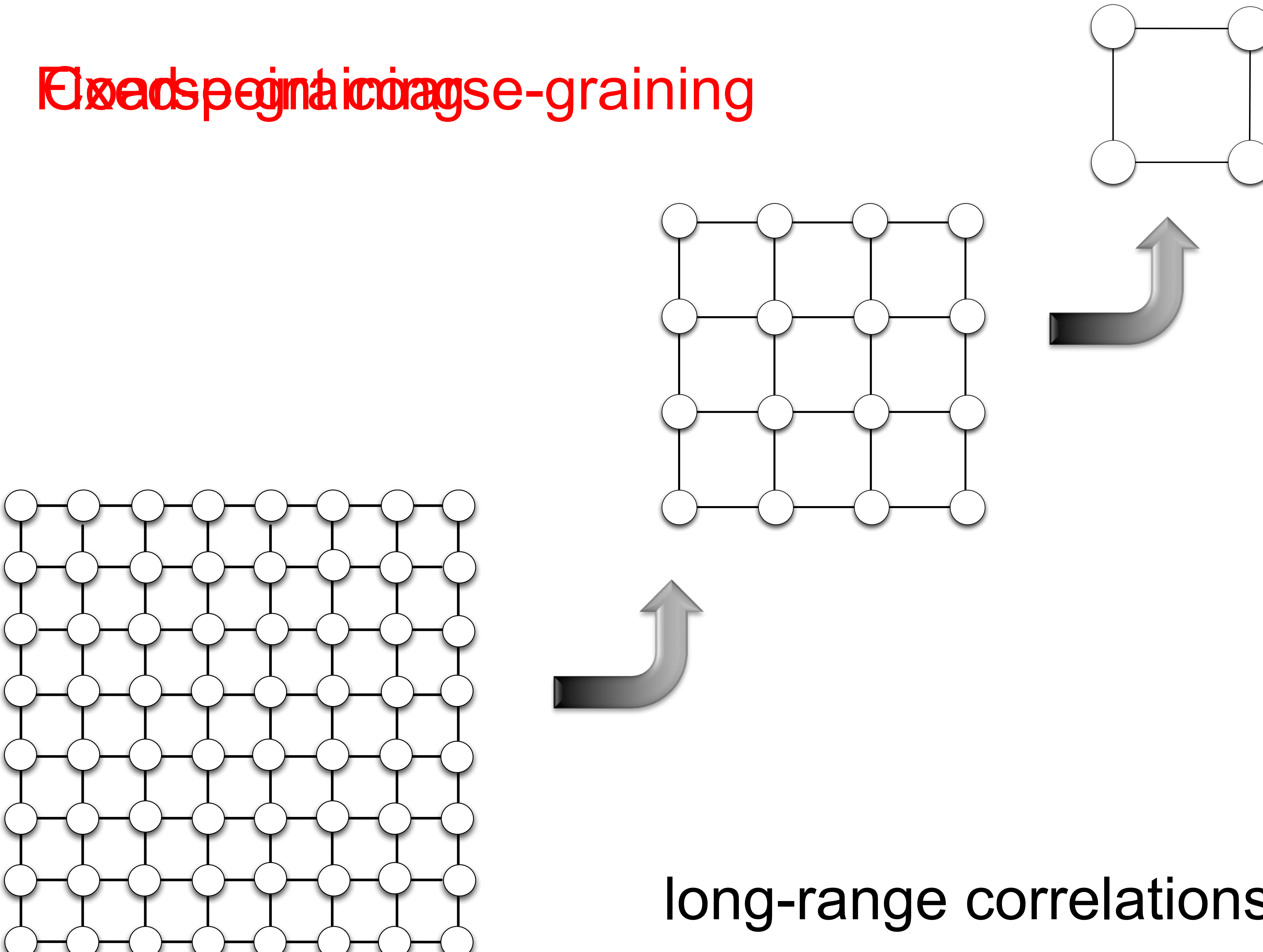



coarse graining



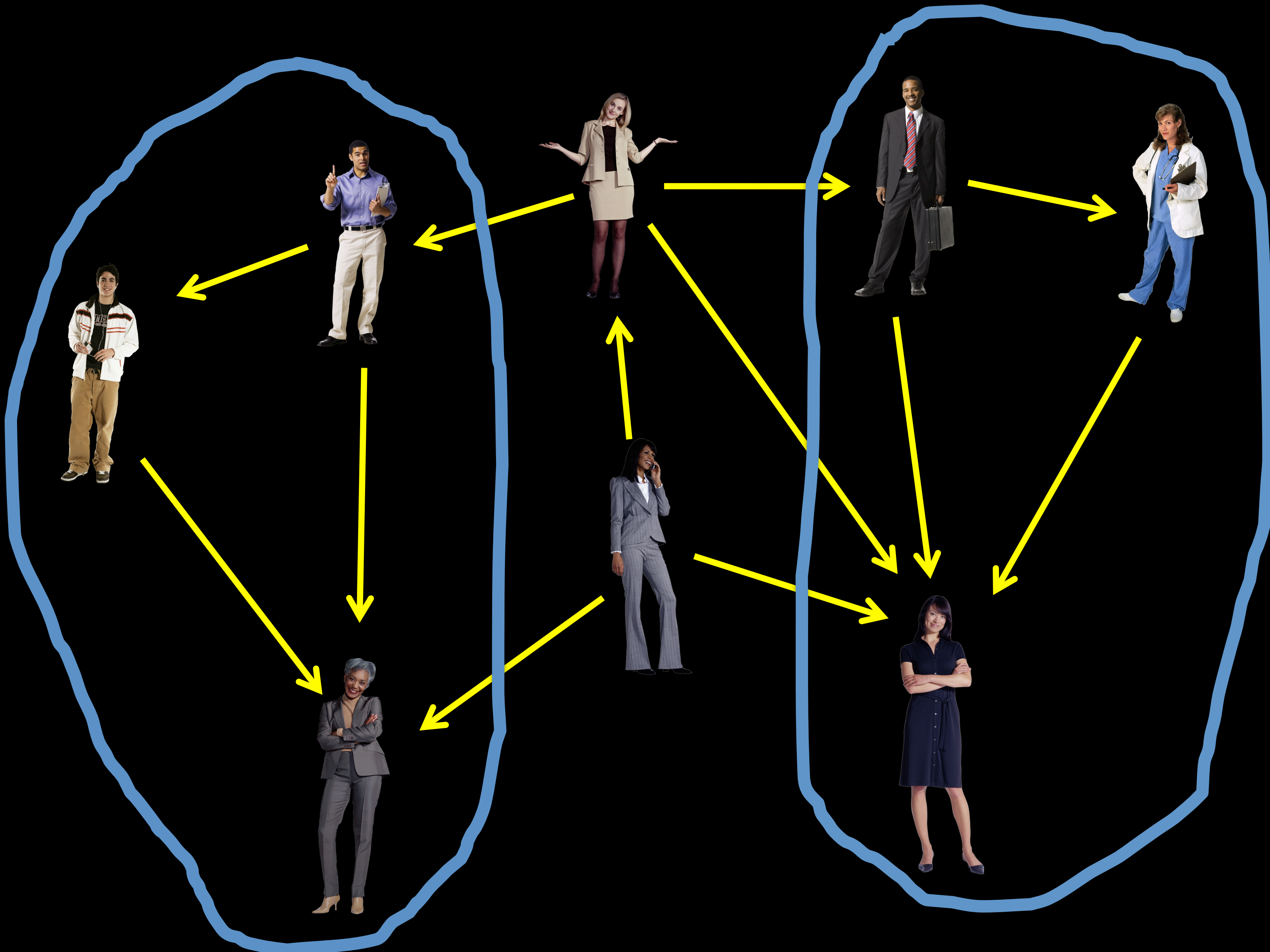
Coarse-graining

Fixed point
Expansion

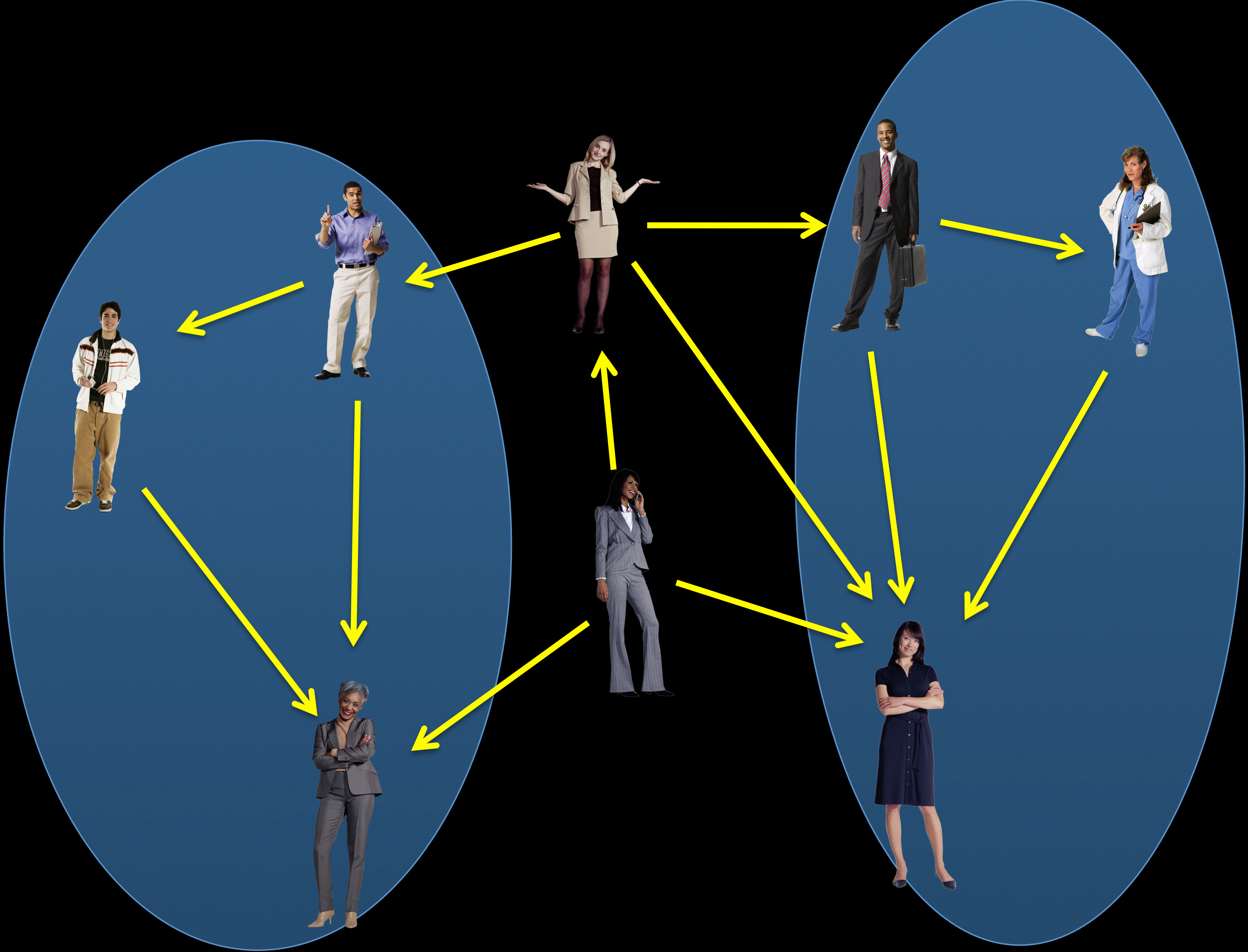


long-range correlations

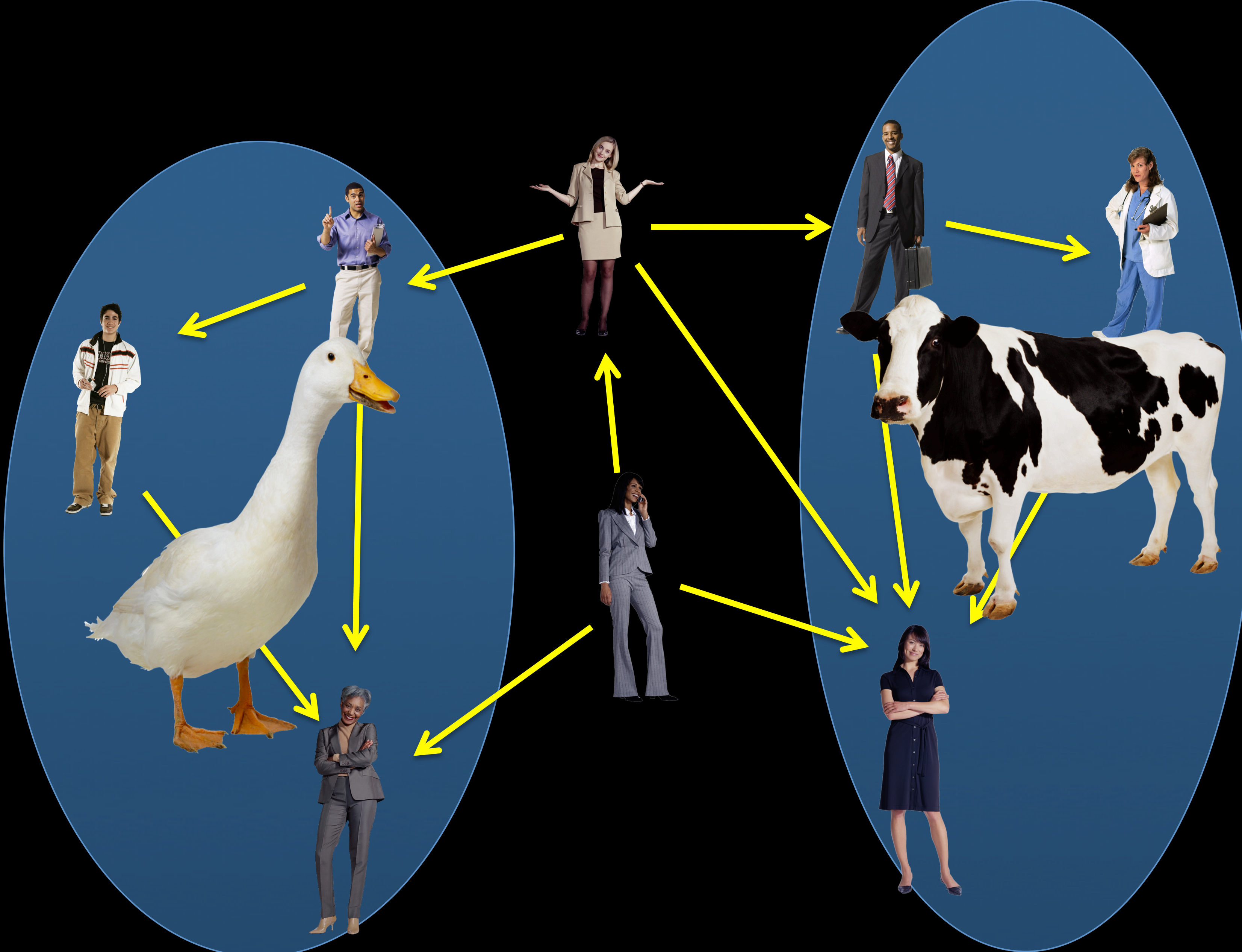
Can we do the same ?

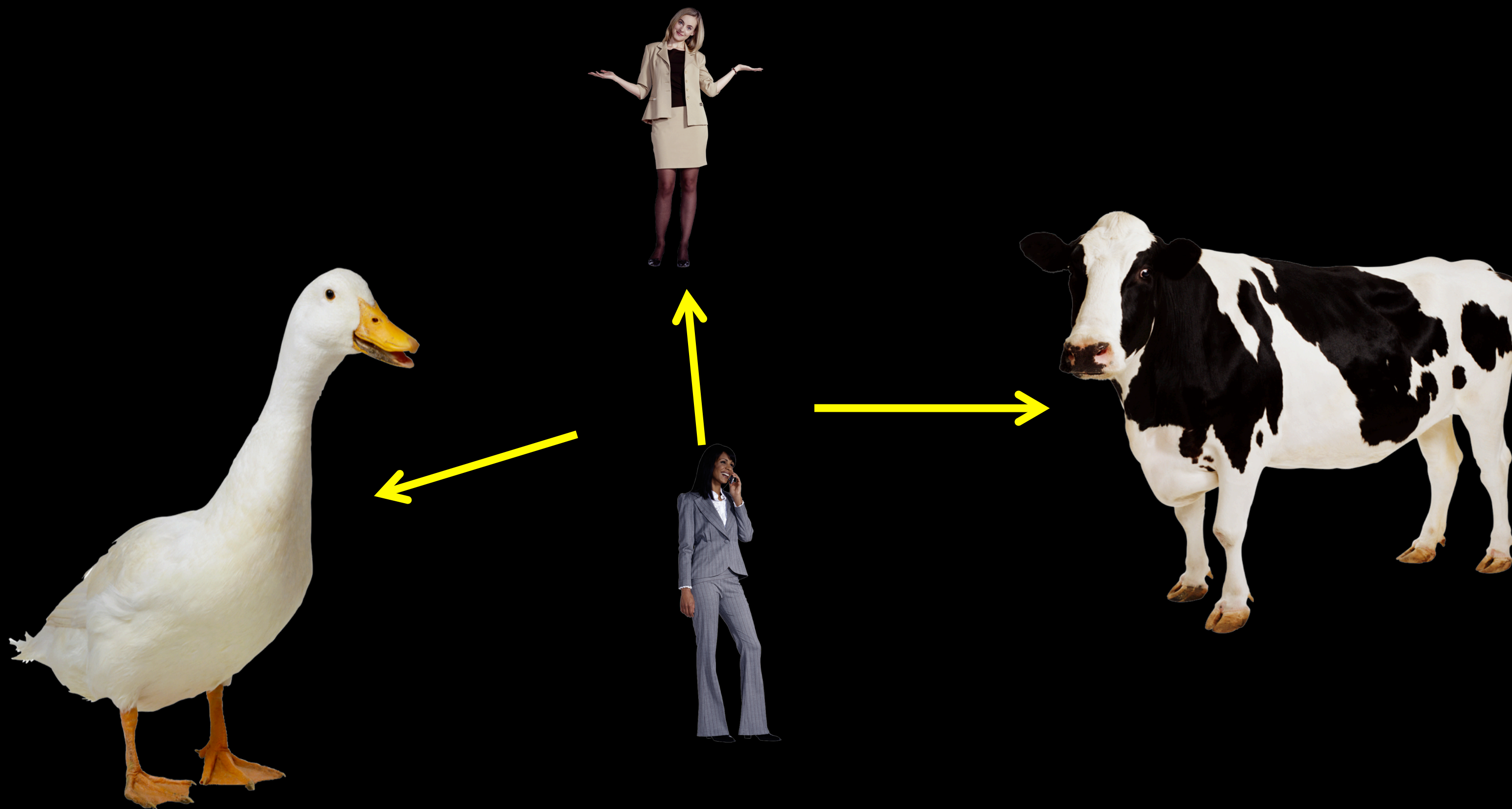


Look out for decoupling

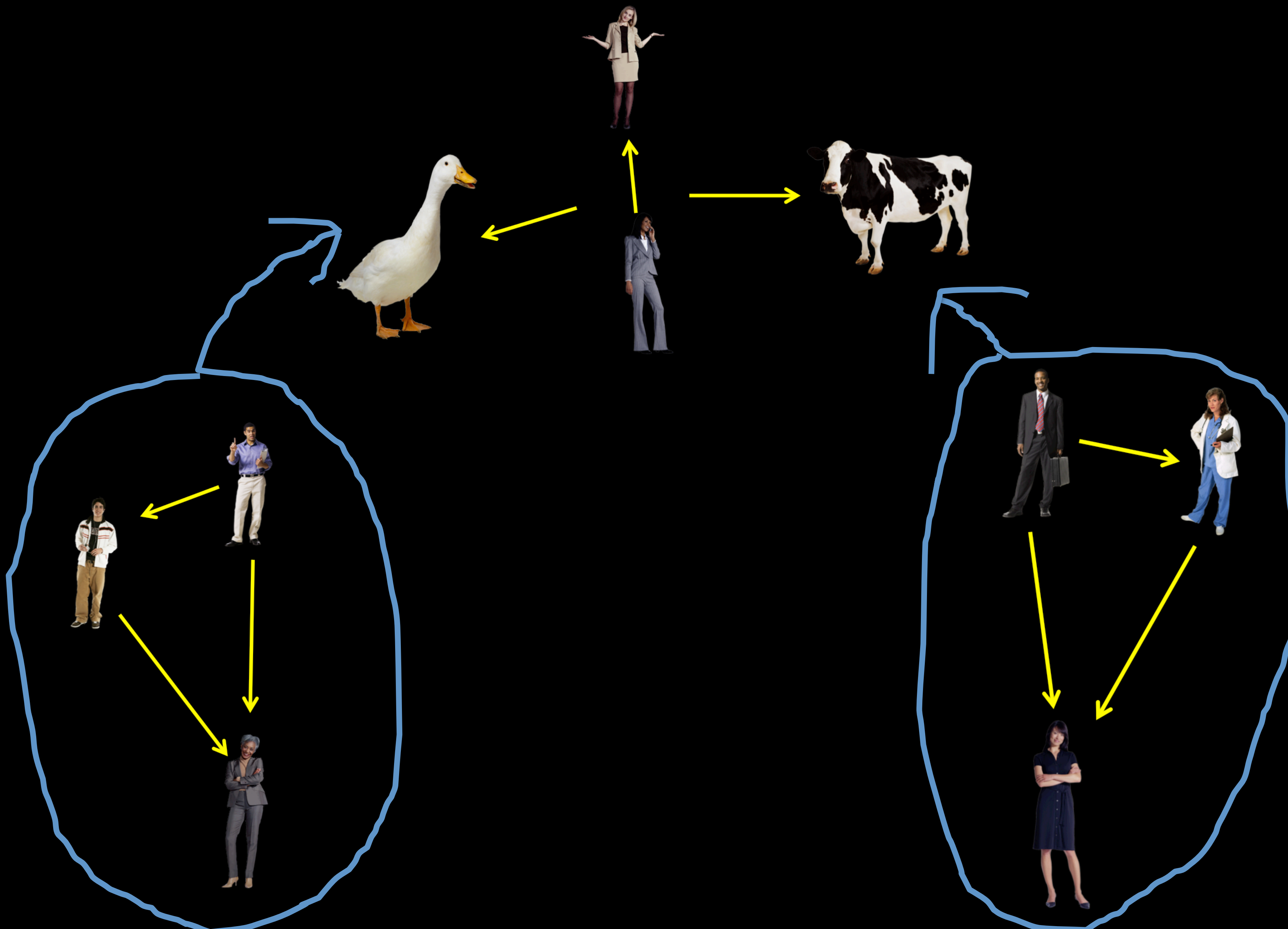


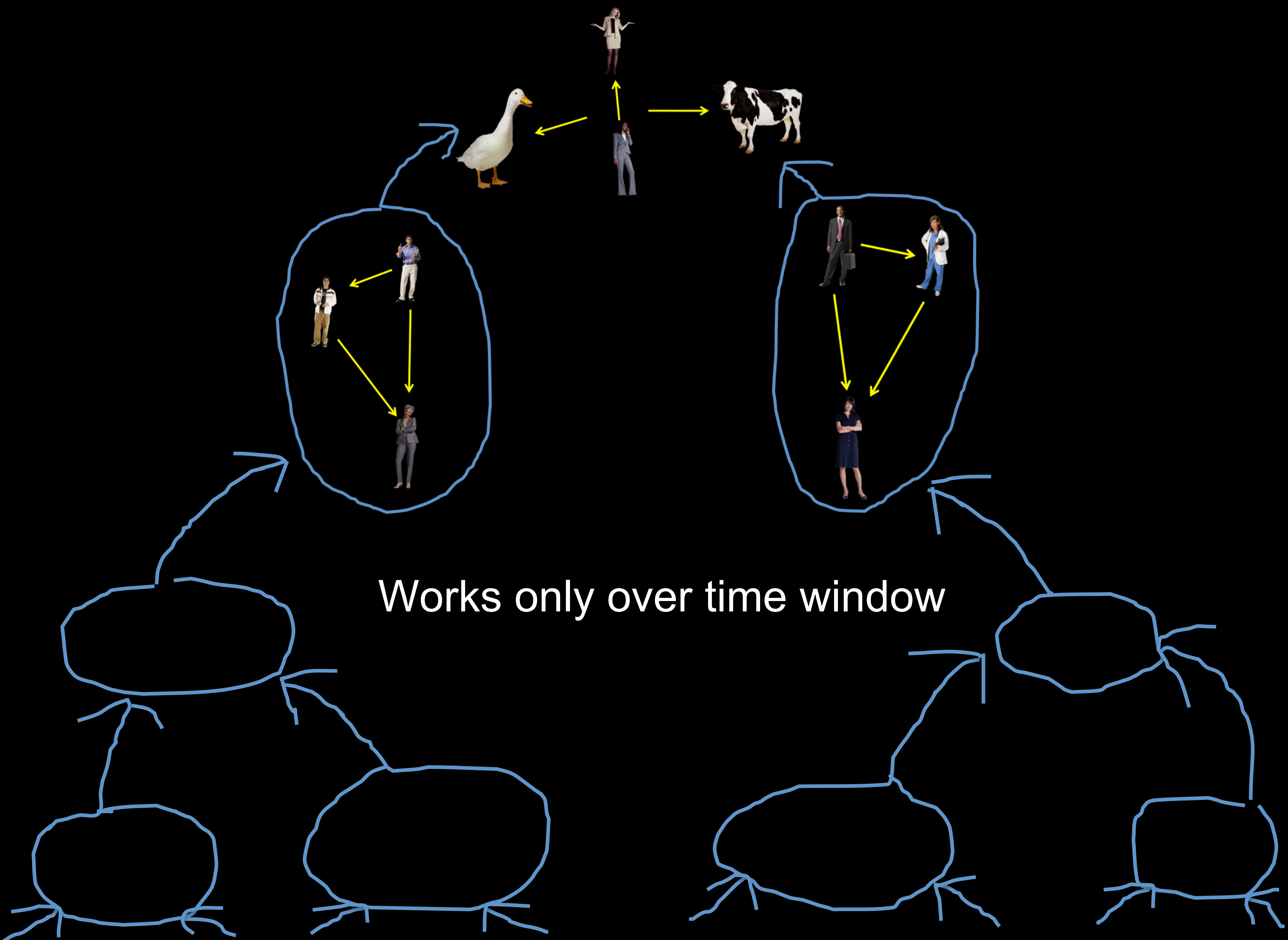
Look out for decoupling



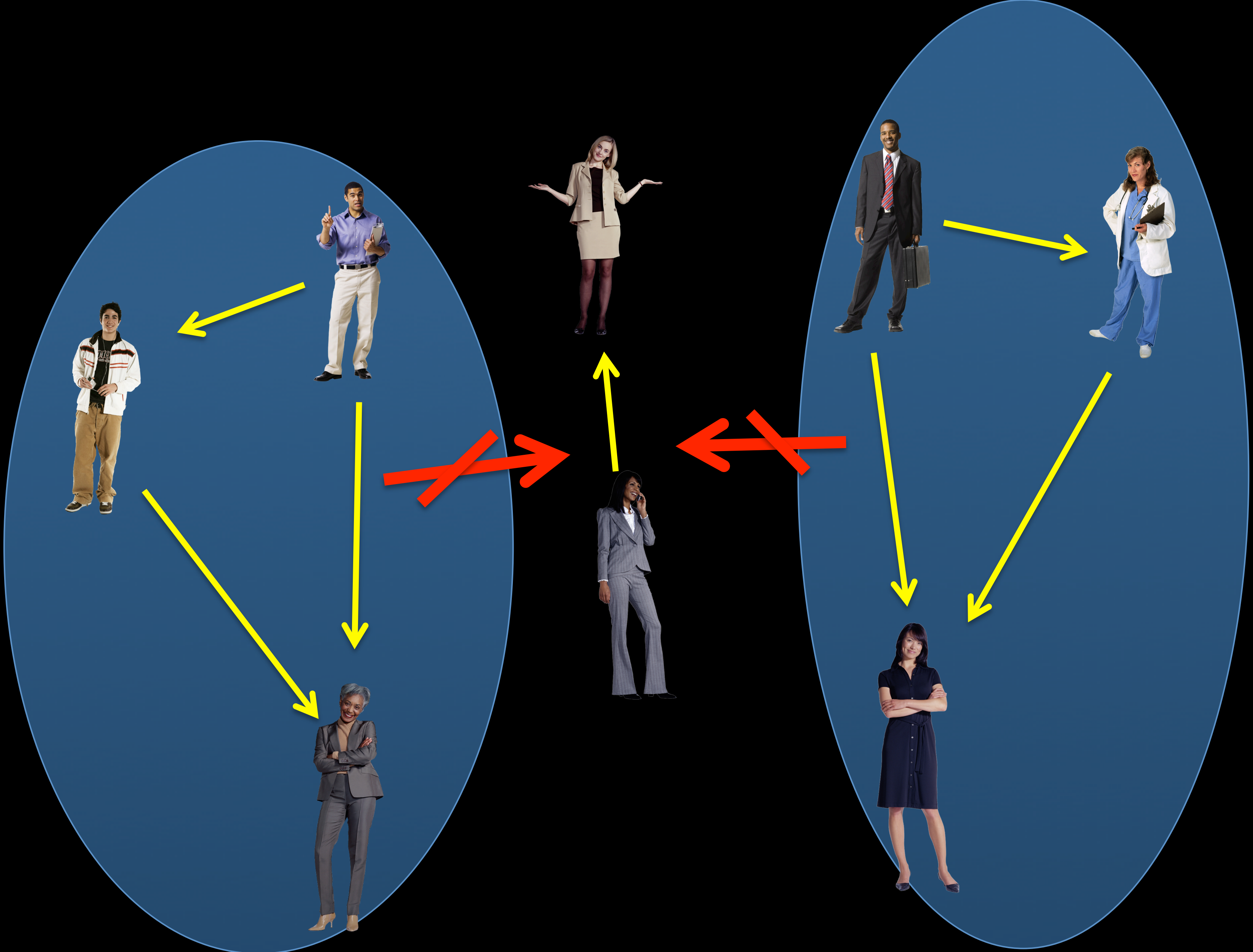


Note the mixing of scales !

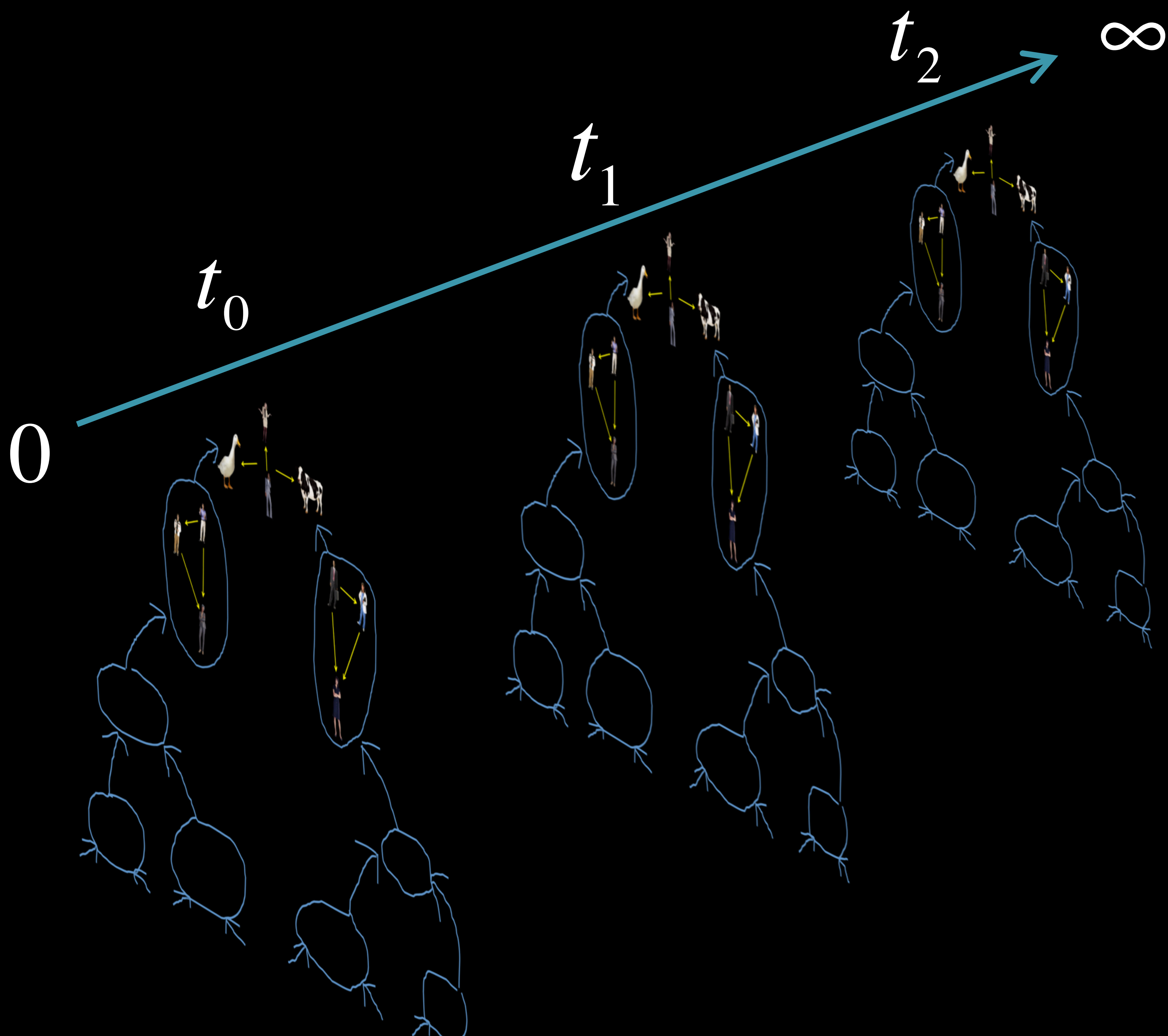




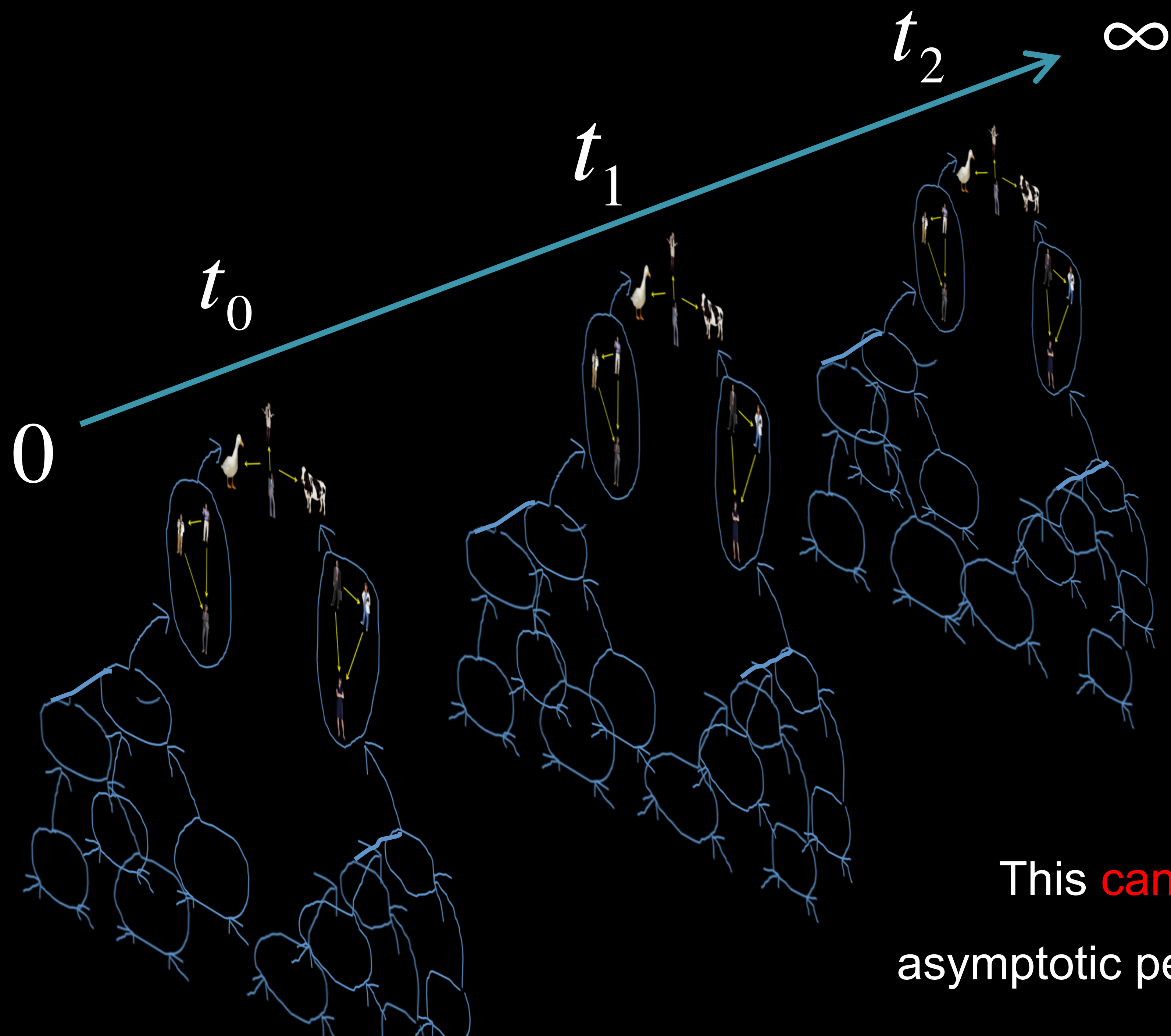
Works only over time window



…. while no red edges

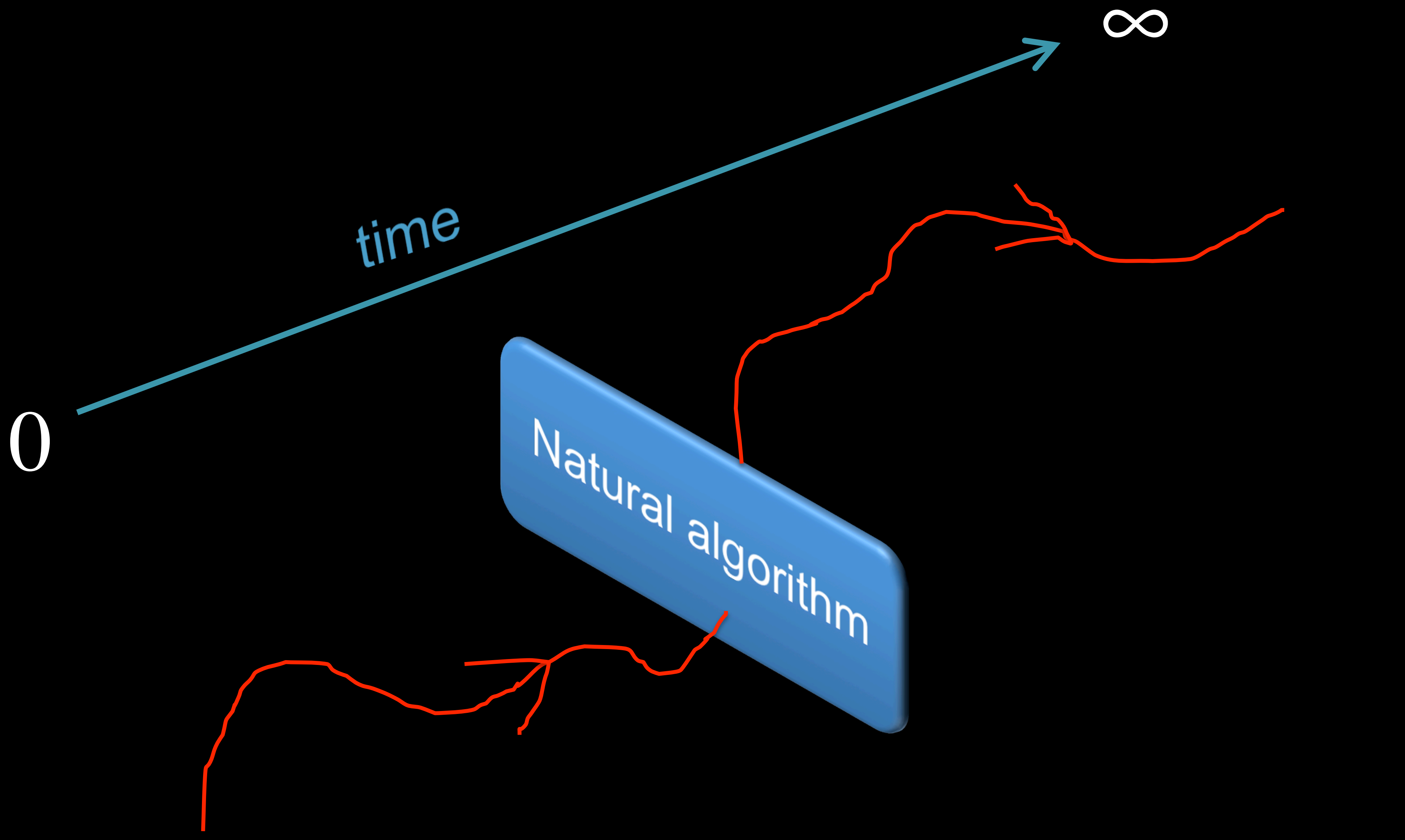


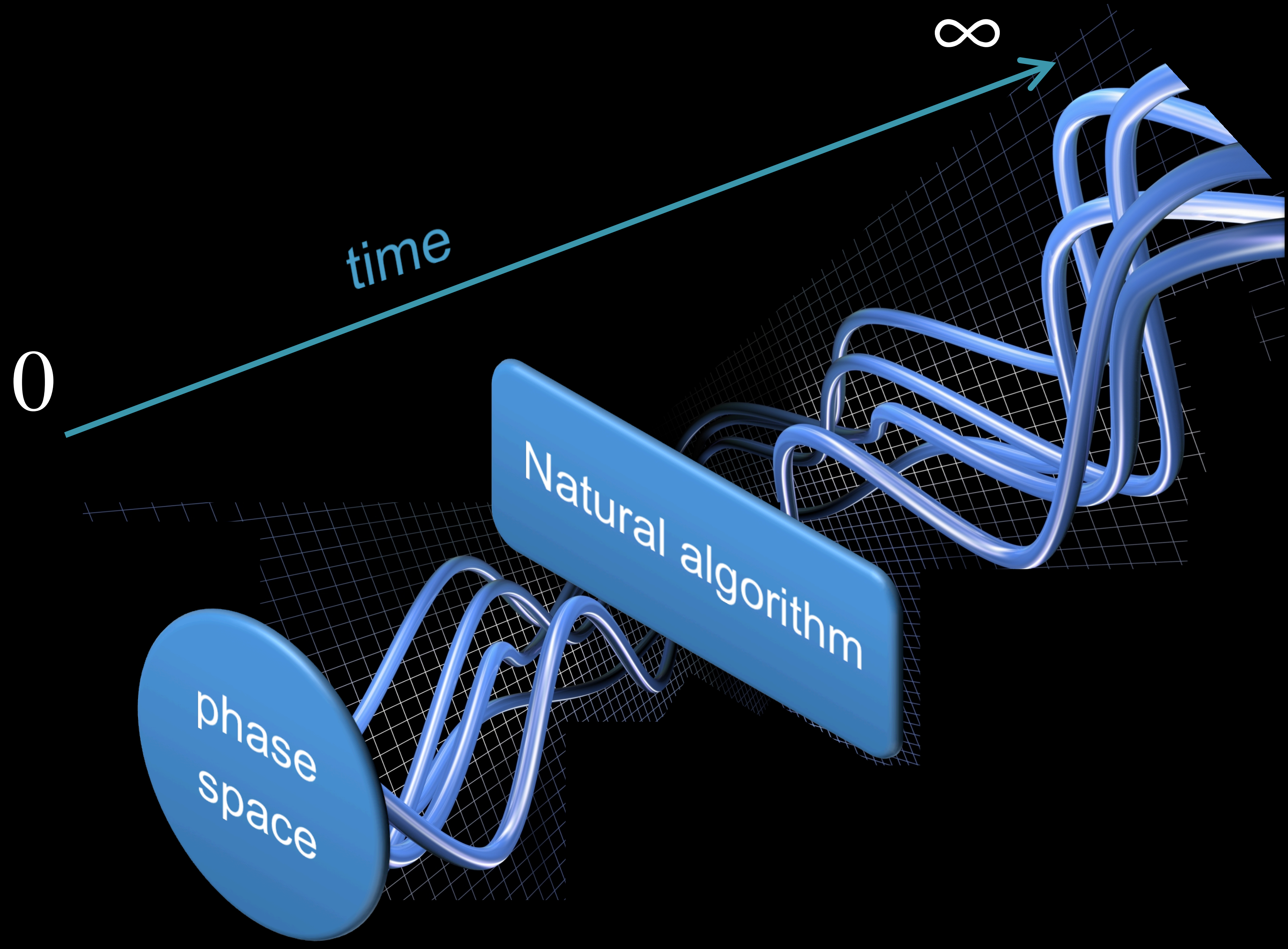
t_2
∞
t_1
t_0
0



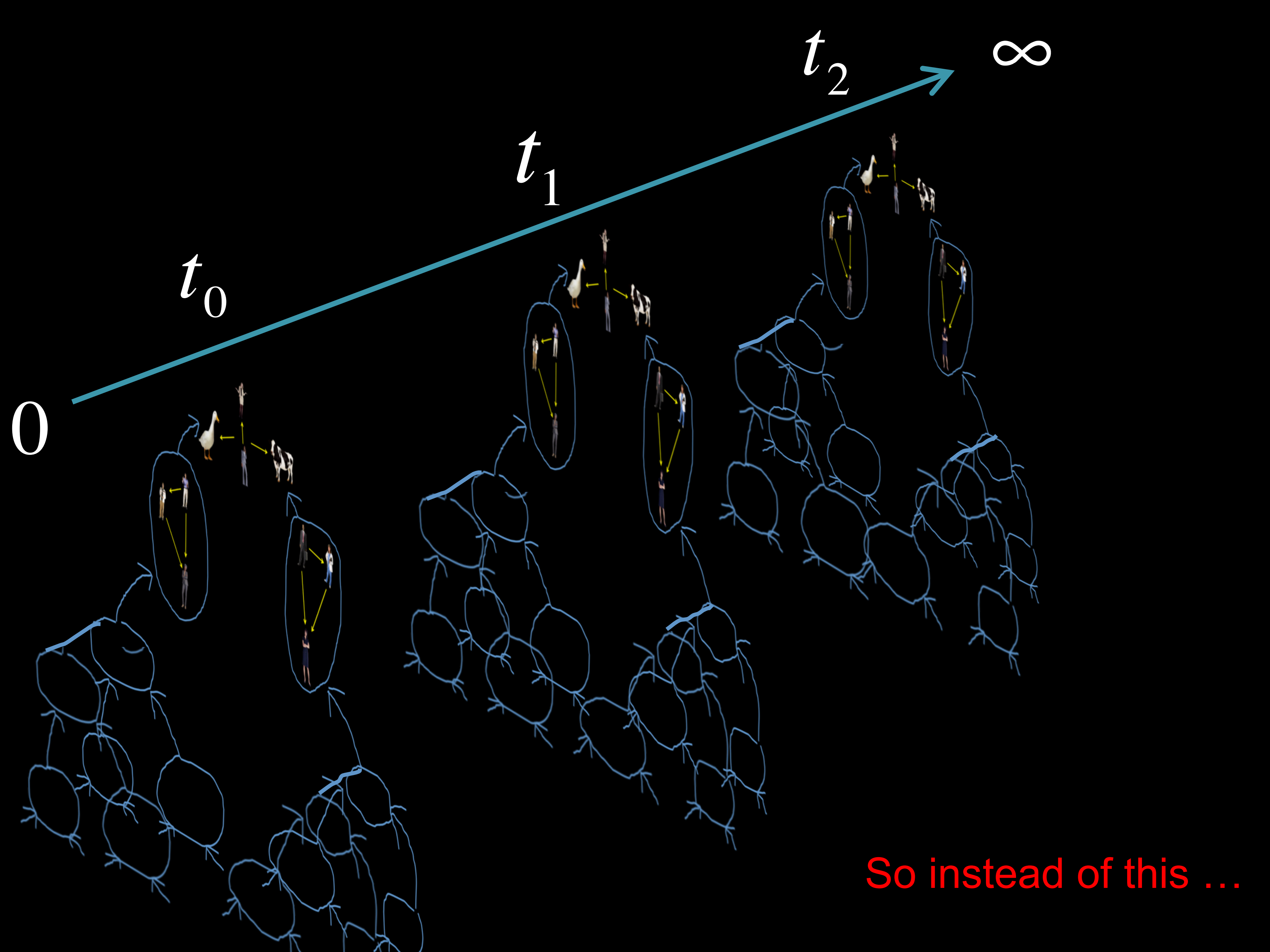
This cannot prove

asymptotic periodicity !

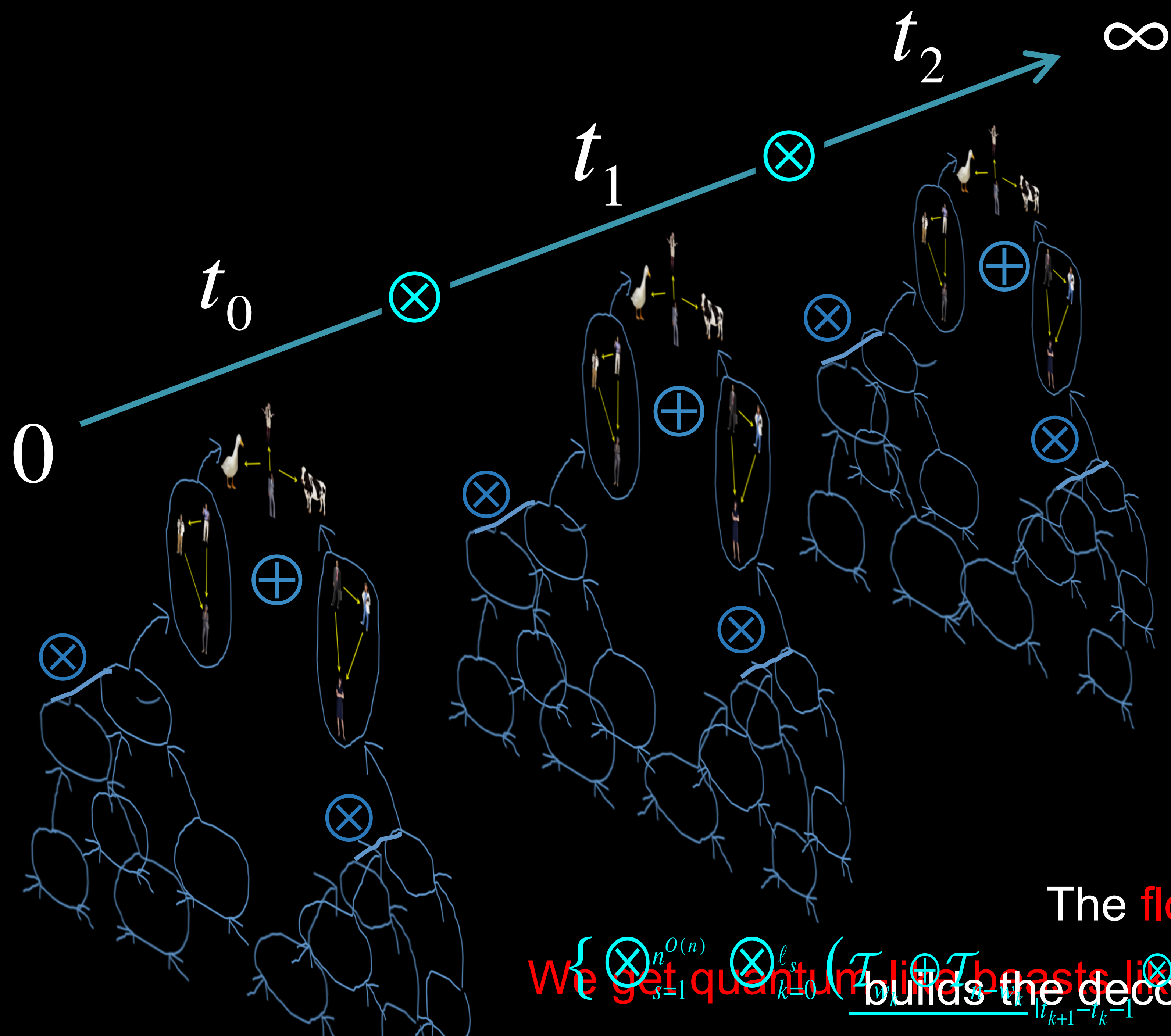

∞
time
0
Natural algorithm



∞
time
0
Natural algorithm
phase
space



t_2
∞
t_1
t_0
0
So instead of this …



The flow tracker builds the decomposition

We get quantum-like beasts like those

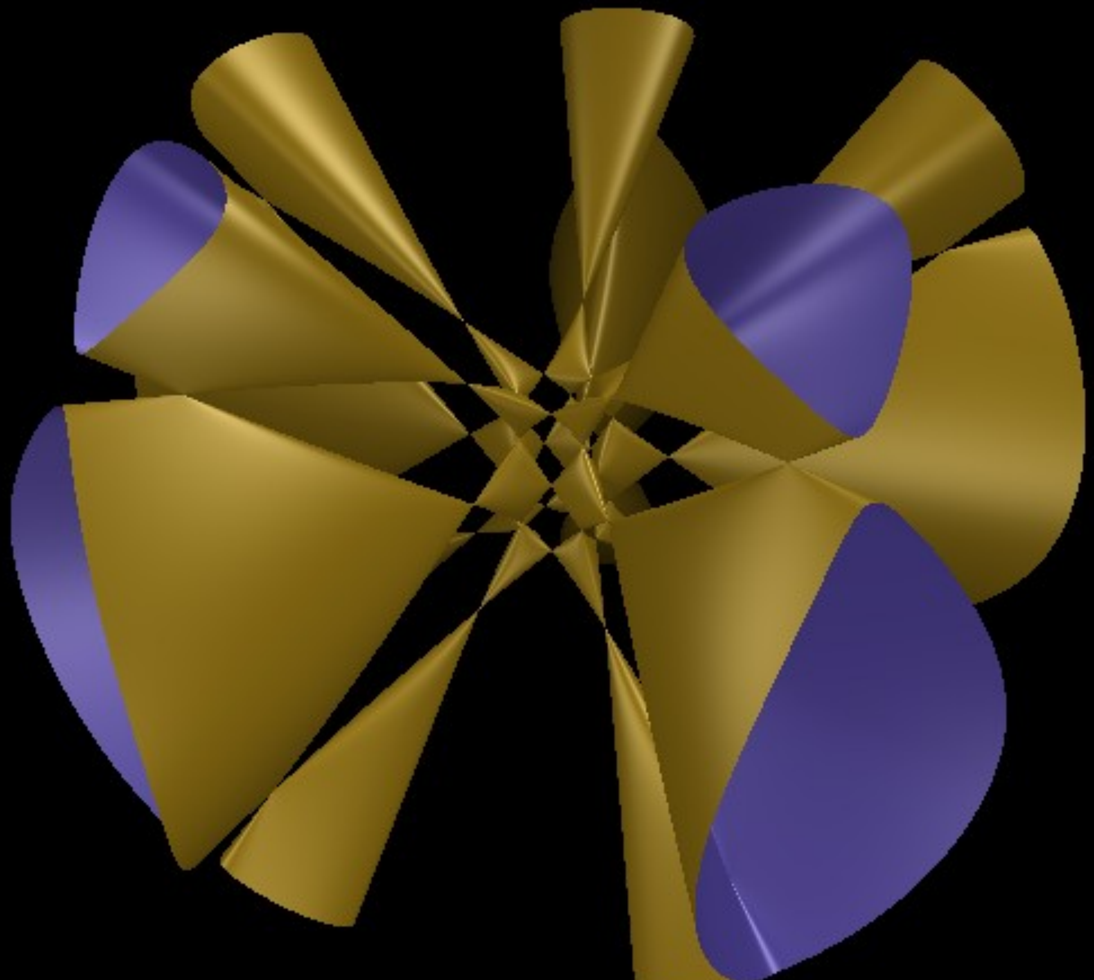
$$\left\{ \bigotimes_{s=1}^{n^{O(n)}} \bigotimes_{k=0}^{\ell_s} \left(\underbrace{\mathcal{T}_{w_k} \oplus \mathcal{T}_{n-w_k}}_{|t_{k+1}-t_k-1} \cdots \otimes \mathcal{T}_n^{|1} \right) \right\} \otimes \mathcal{T}_n^{*}$$

What is phase space ?

n agents, each with d coordinates

Phase space $\boldsymbol{R}^{dn}$

[Tarski-Seidenberg-Collins quantifier elimination]

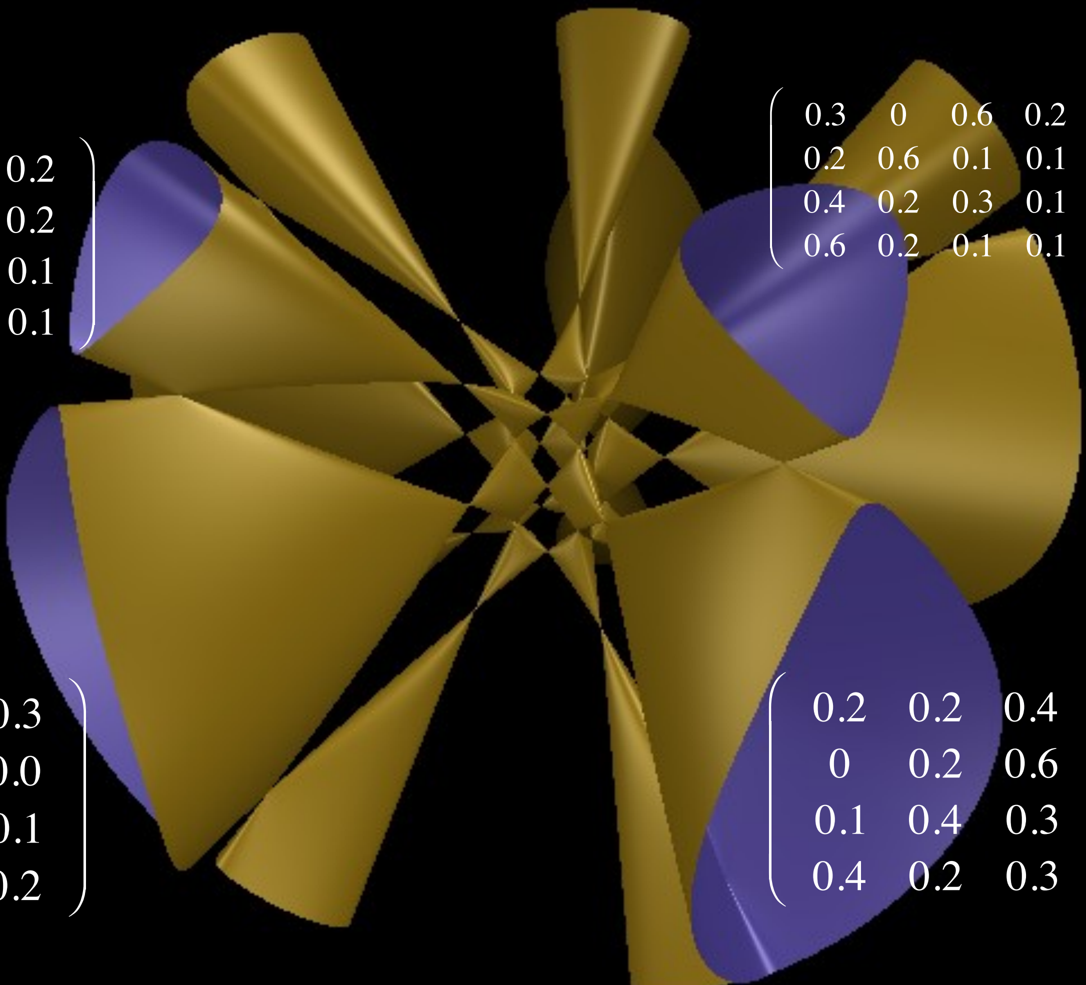


Phase space $\boldsymbol{R}^{dn}$

[Diffusive agent motion]

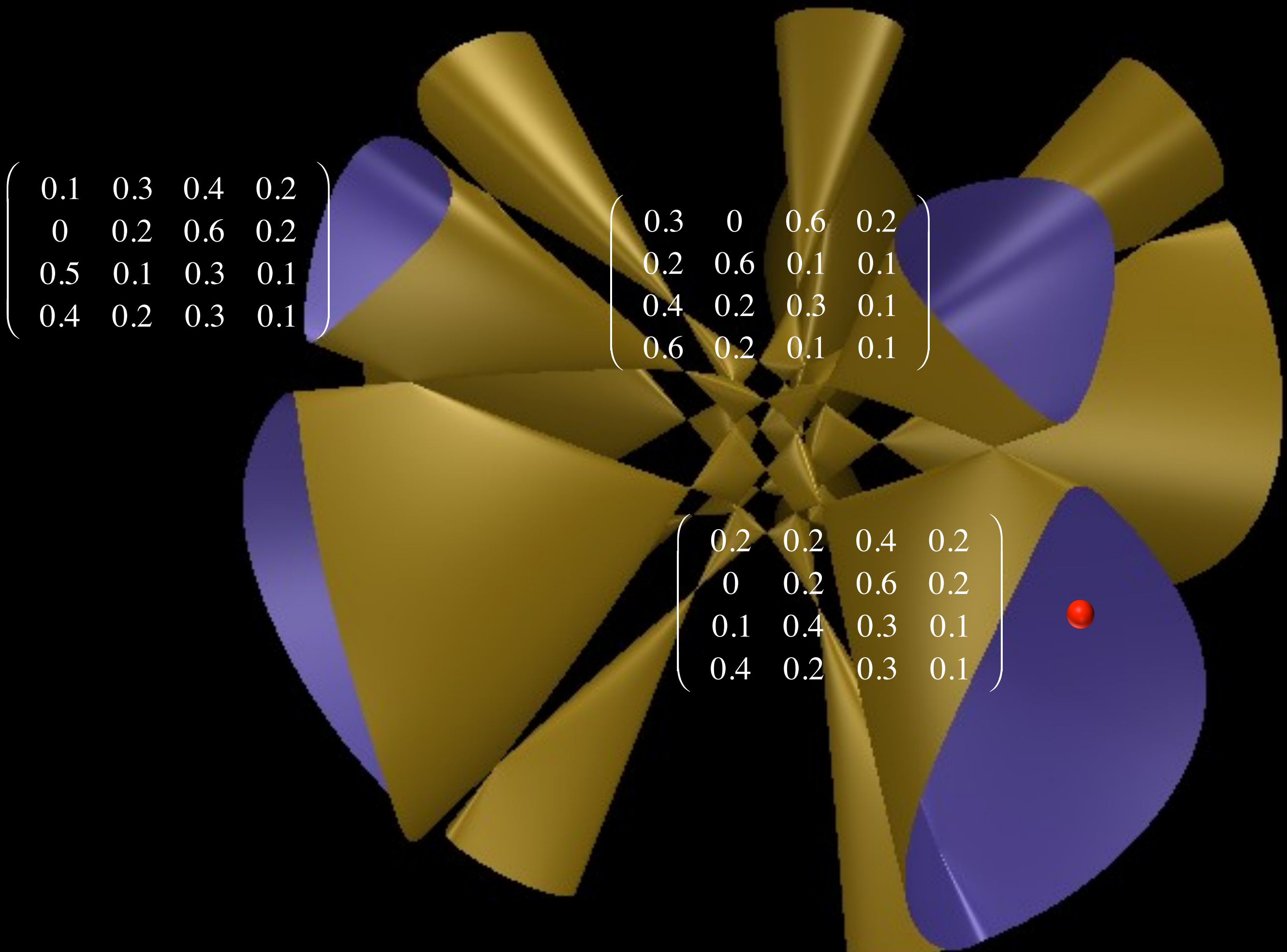
$$\begin{pmatrix} 0.1 & 0.3 & 0.4 & 0.2 \\ 0 & 0.2 & 0.6 & 0.2 \\ 0.5 & 0.1 & 0.3 & 0.1 \\ 0.4 & 0.2 & 0.3 & 0.1 \end{pmatrix}$$

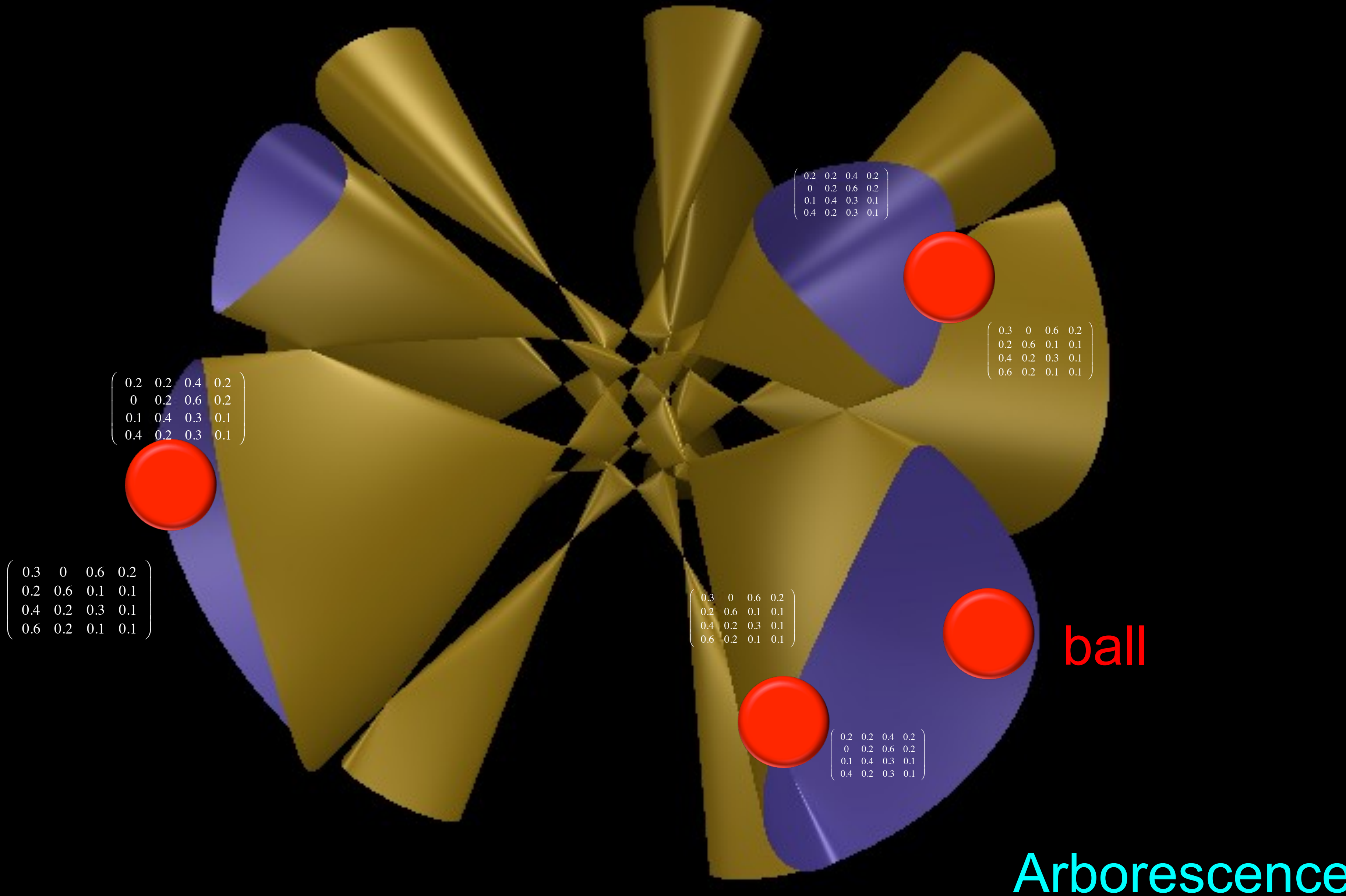
$$\begin{pmatrix} 0.3 & 0 & 0.6 & 0.2 \\ 0.2 & 0.6 & 0.1 & 0.1 \\ 0.4 & 0.2 & 0.3 & 0.1 \\ 0.6 & 0.2 & 0.1 & 0.1 \end{pmatrix}$$



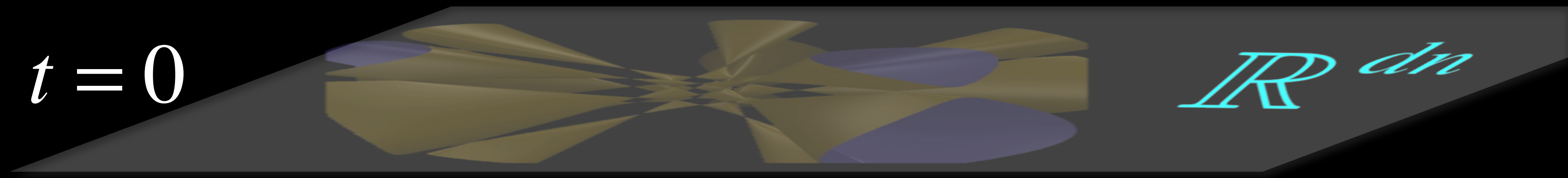
$$\begin{pmatrix} 0.5 & 0 & 0.2 & 0.3 \\ 0.2 & 0.7 & 0.1 & 0.0 \\ 0.4 & 0.2 & 0.3 & 0.1 \\ 0.5 & 0.2 & 0.1 & 0.2 \end{pmatrix}$$

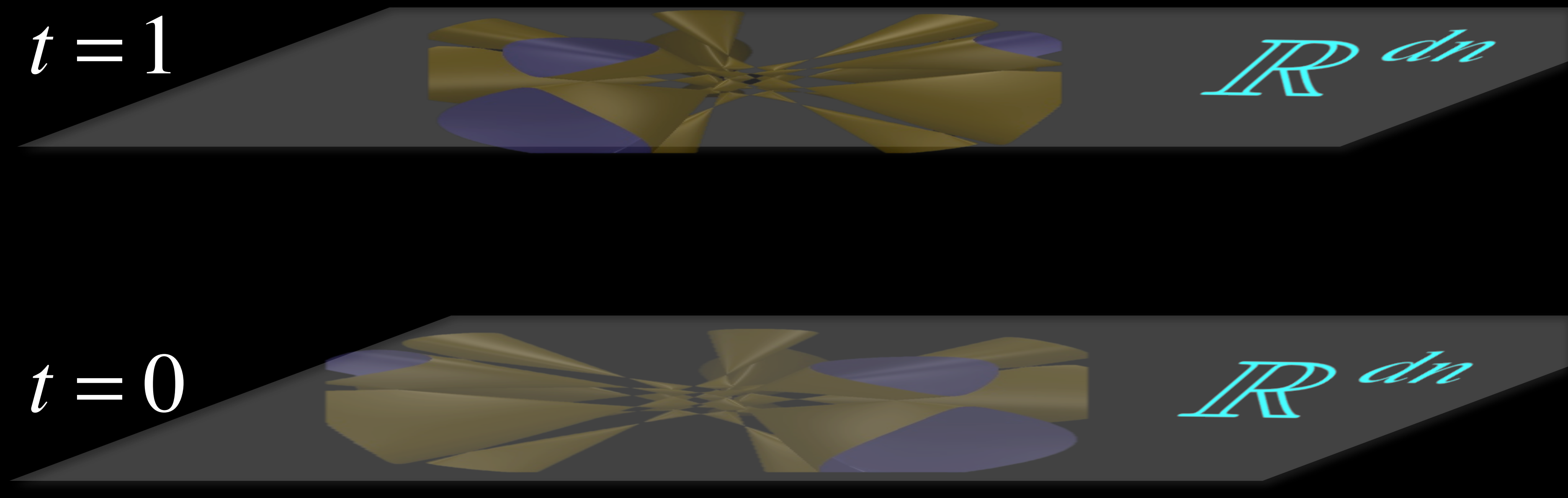
$$\begin{pmatrix} 0.2 & 0.2 & 0.4 & 0.2 \\ 0 & 0.2 & 0.6 & 0.2 \\ 0.1 & 0.4 & 0.3 & 0.1 \\ 0.4 & 0.2 & 0.3 & 0.1 \end{pmatrix}$$

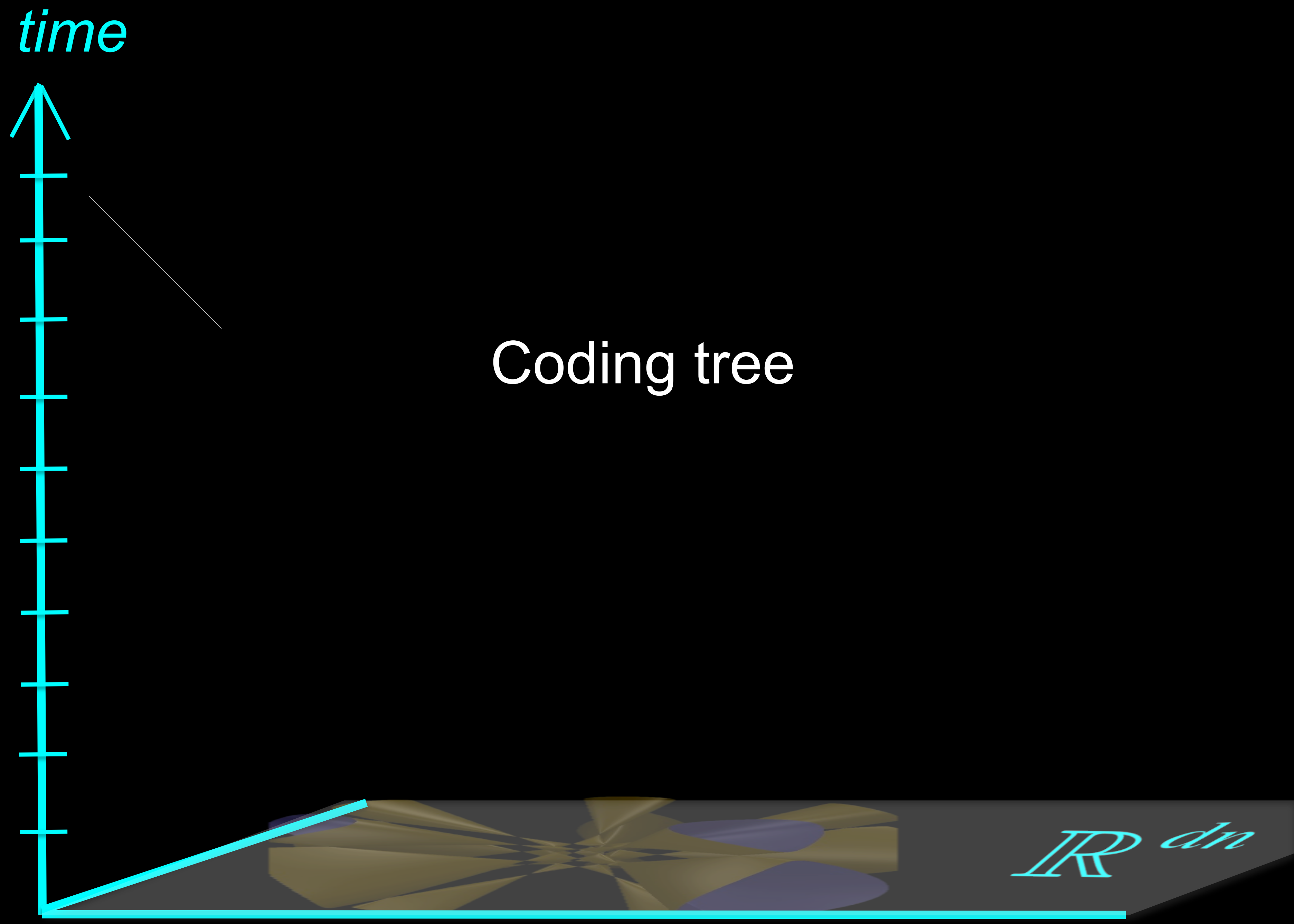

0.1 0.3 0.4 0.2
0 0.2 0.6 0.2
0.5 0.1 0.3 0.1
0.4 0.2 0.3 0.1
0.3 0 0.6 0.2
0.2 0.6 0.1 0.1
0.4 0.2 0.3 0.1
0.6 0.2 0.1 0.1
0.2 0.2 0.4 0.2
0 0.2 0.6 0.2
0.1 0.4 0.3 0.1
0.4 0.2 0.3 0.1


0.2 0.2 0.4 0.2
0 0.2 0.6 0.2
0.1 0.4 0.3 0.1
0.4 0.2 0.3 0.1
0.3 0 0.6 0.2
0.2 0.6 0.1 0.1
0.4 0.2 0.3 0.1
0.6 0.2 0.1 0.1
0.2 0.2 0.4 0.2
0 0.2 0.6 0.2
0.1 0.4 0.3 0.1
0.4 0.2 0.3 0.1
0.3 0 0.6 0.2
0.2 0.6 0.1 0.1
0.4 0.2 0.3 0.1
0.6 0.2 0.1 0.1
0.3 0 0.6 0.2
0.2 0.6 0.1 0.1
0.4 0.2 0.3 0.1
0.6 0.2 0.1 0.1
0.2 0.2 0.4 0.2
0 0.2 0.6 0.2
0.1 0.4 0.3 0.1
0.4 0.2 0.3 0.1
ball
Arborescence

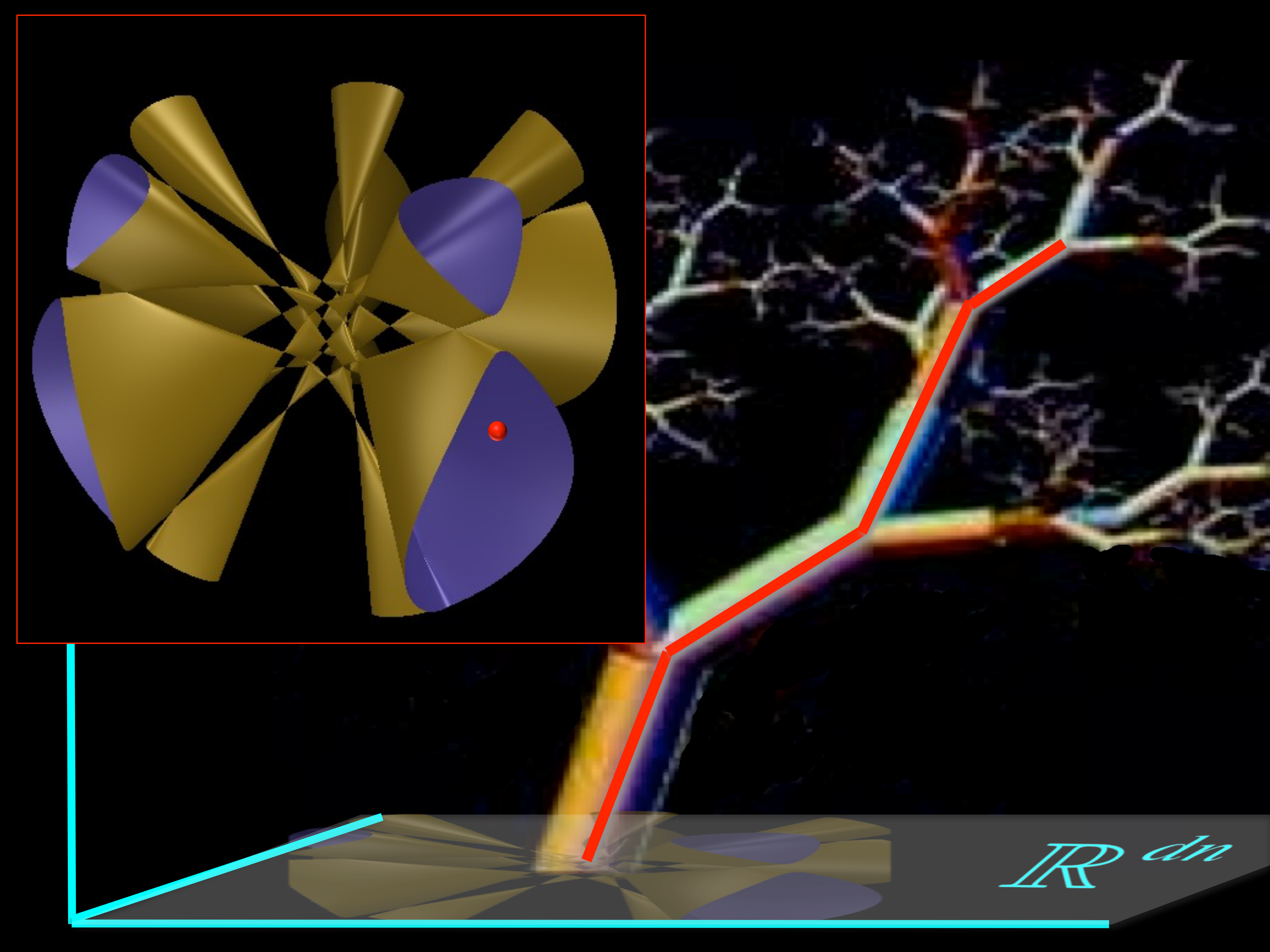
$t = 0$




$t = 1$
$\mathbb{R}^{dn}$
$t = 0$
$\mathbb{R}^{dn}$


time
Coding tree
$\mathbb{R}^{dn}$

time
$\mathbb{R}^{dn}$


$\mathbb{R}^{dn}$

The coding tree has all the answers

Criticality

branching

thinning

entropy

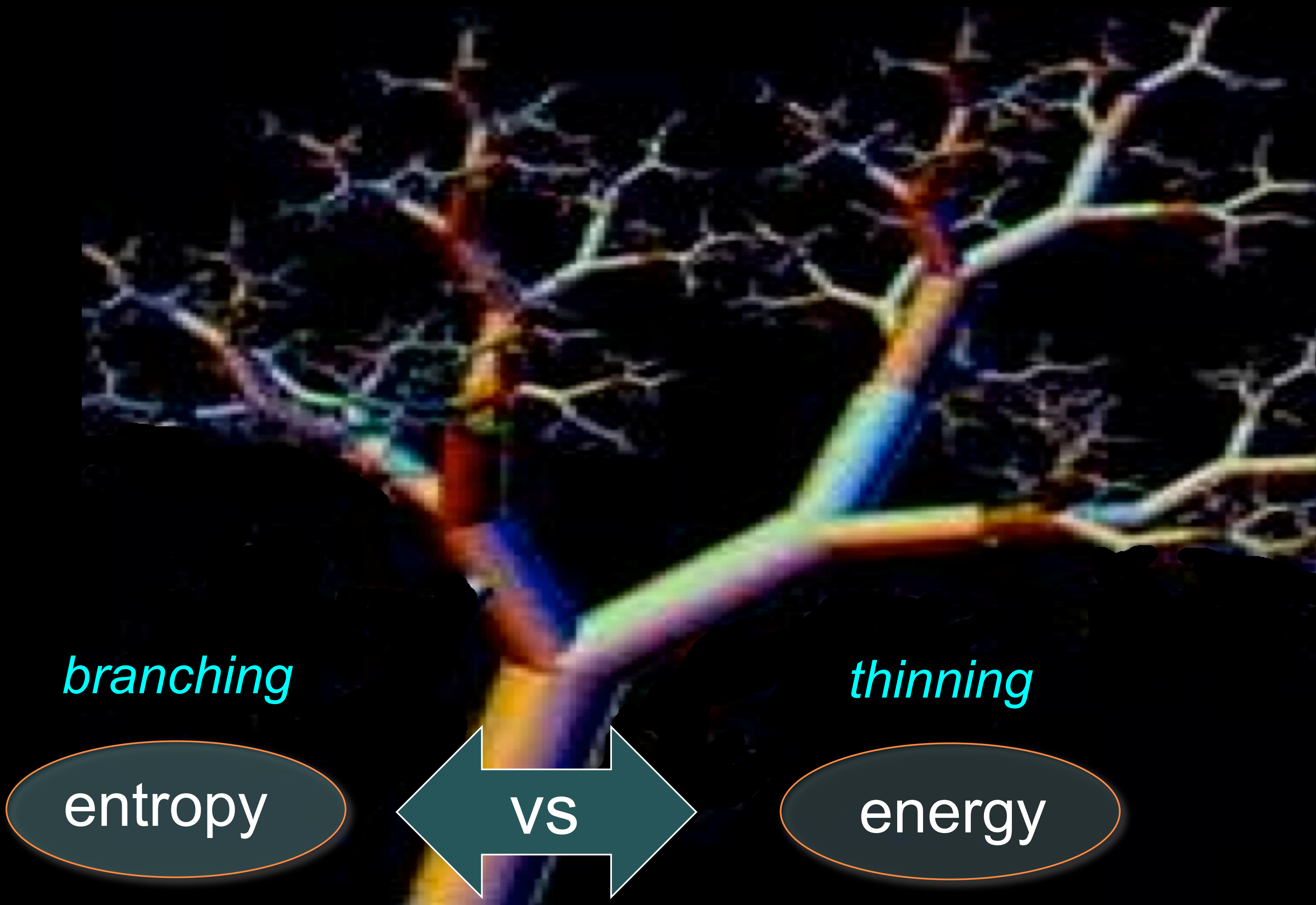
vs

energy

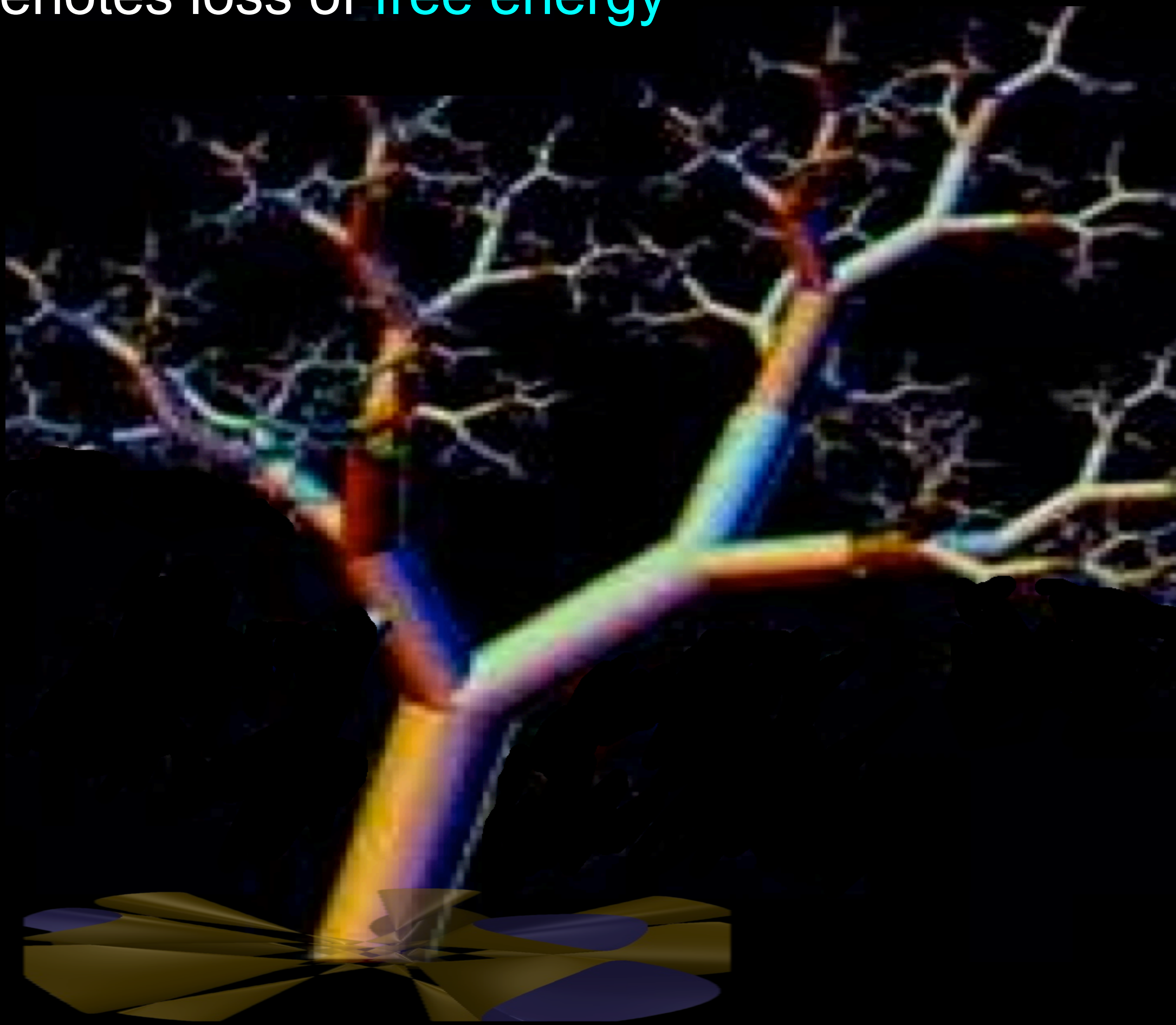
“ matrix rigidity ” argument

Entropy $= \lim_{k\to\infty} \frac{1}{k} \log$ # paths of length k $= 0$ almost surely

Criticality



Thinning denotes loss of free energy



For periodicity, we hope to see this …

Principal eigenspace can oscillate

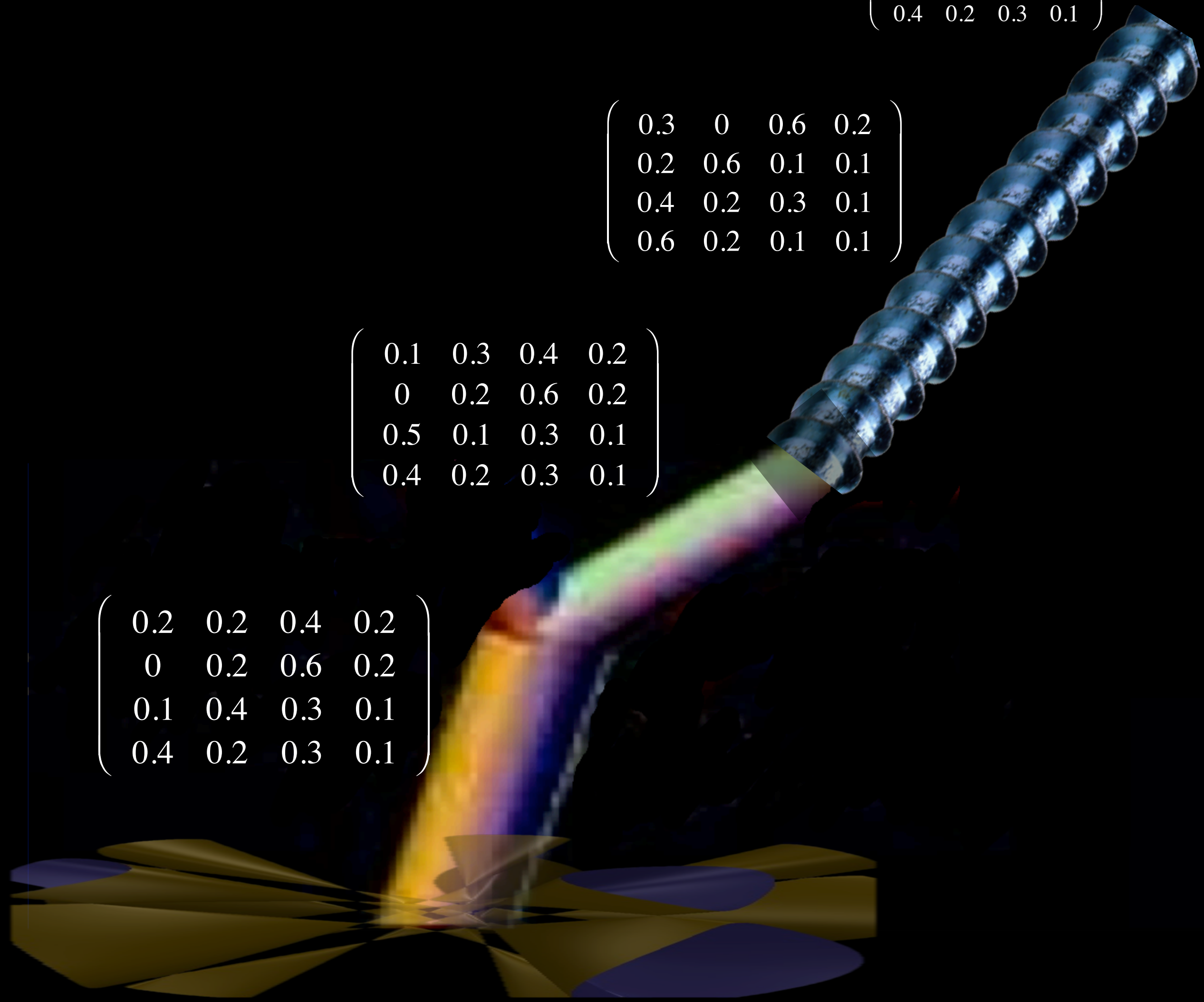
but we may get this ...

$$\begin{pmatrix} 0.2 & 0.2 & 0.4 & 0.2 \\ 0 & 0.2 & 0.6 & 0.2 \\ 0.1 & 0.4 & 0.3 & 0.1 \\ 0.4 & 0.2 & 0.3 & 0.1 \end{pmatrix}$$

$$\begin{pmatrix} 0.3 & 0 & 0.6 & 0.2 \\ 0.2 & 0.6 & 0.1 & 0.1 \\ 0.4 & 0.2 & 0.3 & 0.1 \\ 0.6 & 0.2 & 0.1 & 0.1 \end{pmatrix}$$

$$\begin{pmatrix} 0.1 & 0.3 & 0.4 & 0.2 \\ 0 & 0.2 & 0.6 & 0.2 \\ 0.5 & 0.1 & 0.3 & 0.1 \\ 0.4 & 0.2 & 0.3 & 0.1 \end{pmatrix}$$

$$\begin{pmatrix} 0.2 & 0.2 & 0.4 & 0.2 \\ 0 & 0.2 & 0.6 & 0.2 \\ 0.1 & 0.4 & 0.3 & 0.1 \\ 0.4 & 0.2 & 0.3 & 0.1 \end{pmatrix}$$



s-energy [C '10]

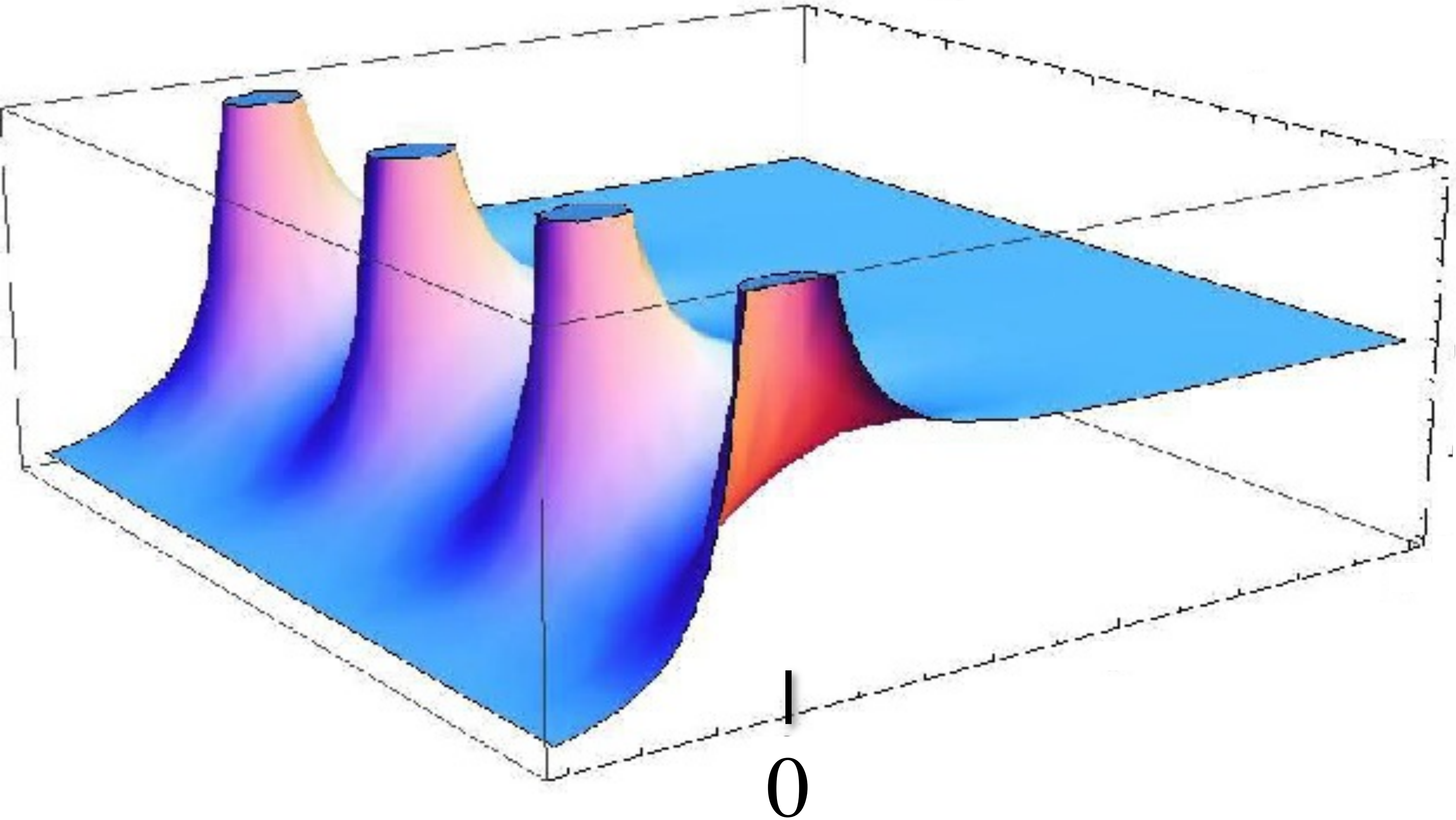
- Infinite set of stochastic matrices $P_0, P_1, \ldots$
- Let G_t denote the graph induced by P_t

$$E(x,s) = \sum_{t=0}^{\infty} \sum_{(i,j)\in G_t} |(P_t \cdots P_0 x)_i - (P_t \cdots P_0 x)_j|^s$$

$$E(x,s) = \sum_{t=0}^{\infty} \sum_{(i,j)\in G_t} |(P_t \cdots P_0\, x)_i - (P_t \cdots P_0\, x)_j|^s$$

- Dirichlet series (invertible !)
- Bounds on s-energy [C'10]
- $E(x,0) = \infty$

Idea is to pick s near 0 and derive Chernoff-like bounds on mixing

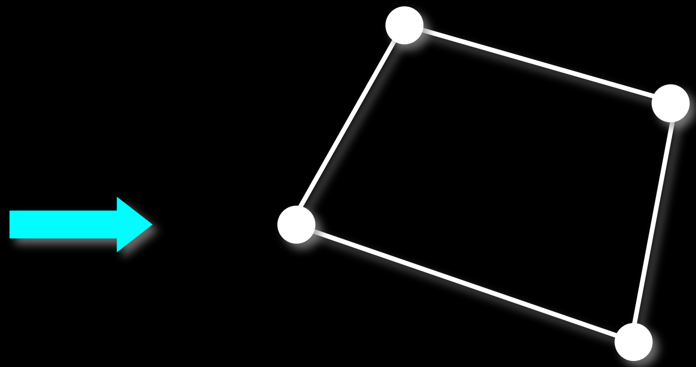

0

$$\begin{pmatrix} 0.3 & 0.2 & 0 & 0.5 \\ 0.1 & 0.4 & 0.4 & 0.1 \\ 0 & 0.9 & 0.1 & 0 \\ 0.6 & 0.1 & 0 & 0.3 \end{pmatrix}$$

$$\begin{pmatrix} 0.3 & 0.2 & 0 & 0.5 \\ 0.1 & 0.4 & 0.4 & 0.1 \\ 0 & 0.9 & 0.1 & 0 \\ 0.6 & 0.1 & 0 & 0.3 \end{pmatrix}$$

in R^4

$$\begin{pmatrix} 0.3 & 0.2 & 0 & 0.5 \\ 0.1 & 0.4 & 0.4 & 0.1 \\ 0 & 0.9 & 0.1 & 0 \\ 0.6 & 0.1 & 0 & 0.3 \end{pmatrix}$$



$P_1 \rightarrow$

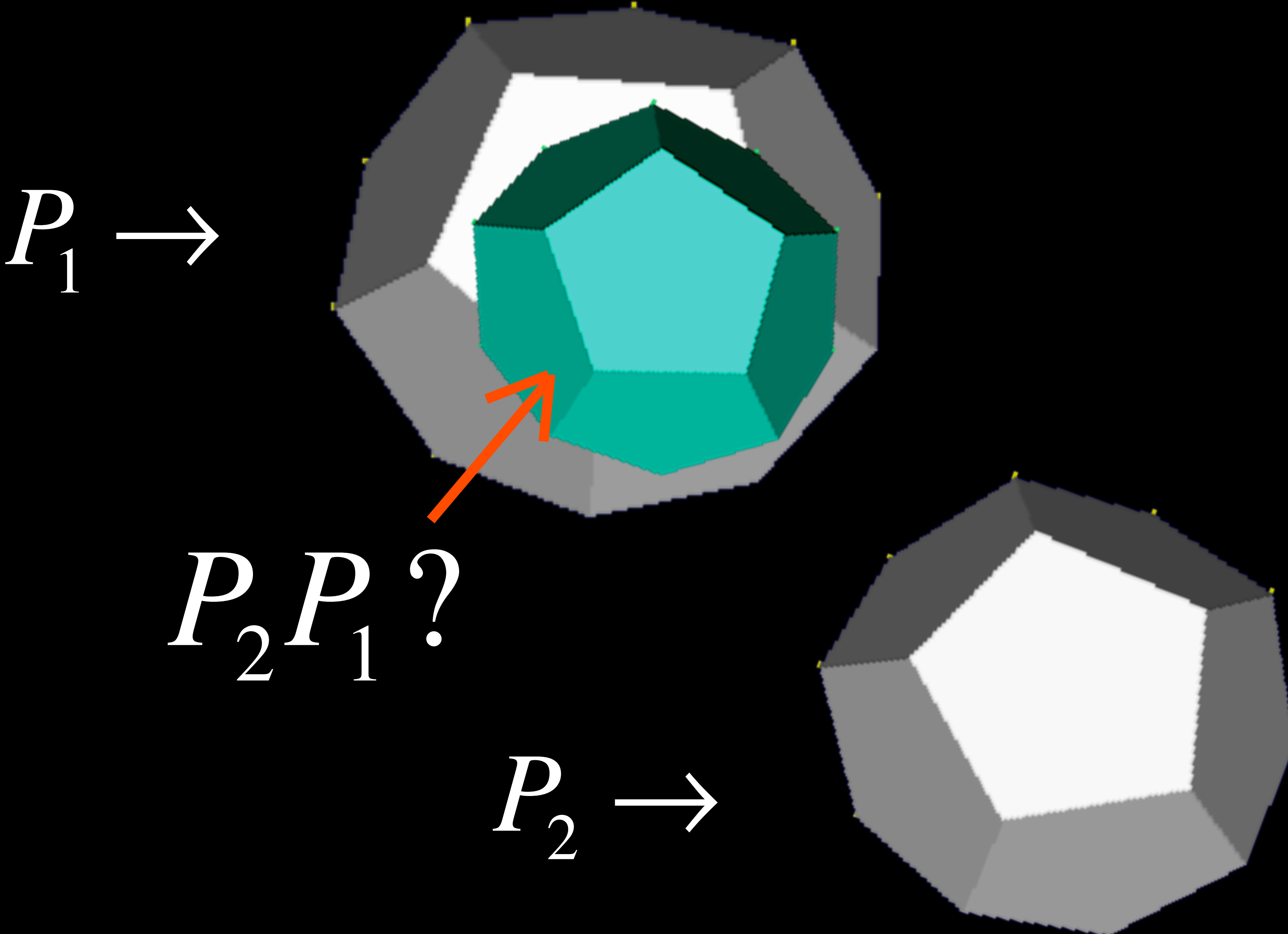
$P_1 \rightarrow$

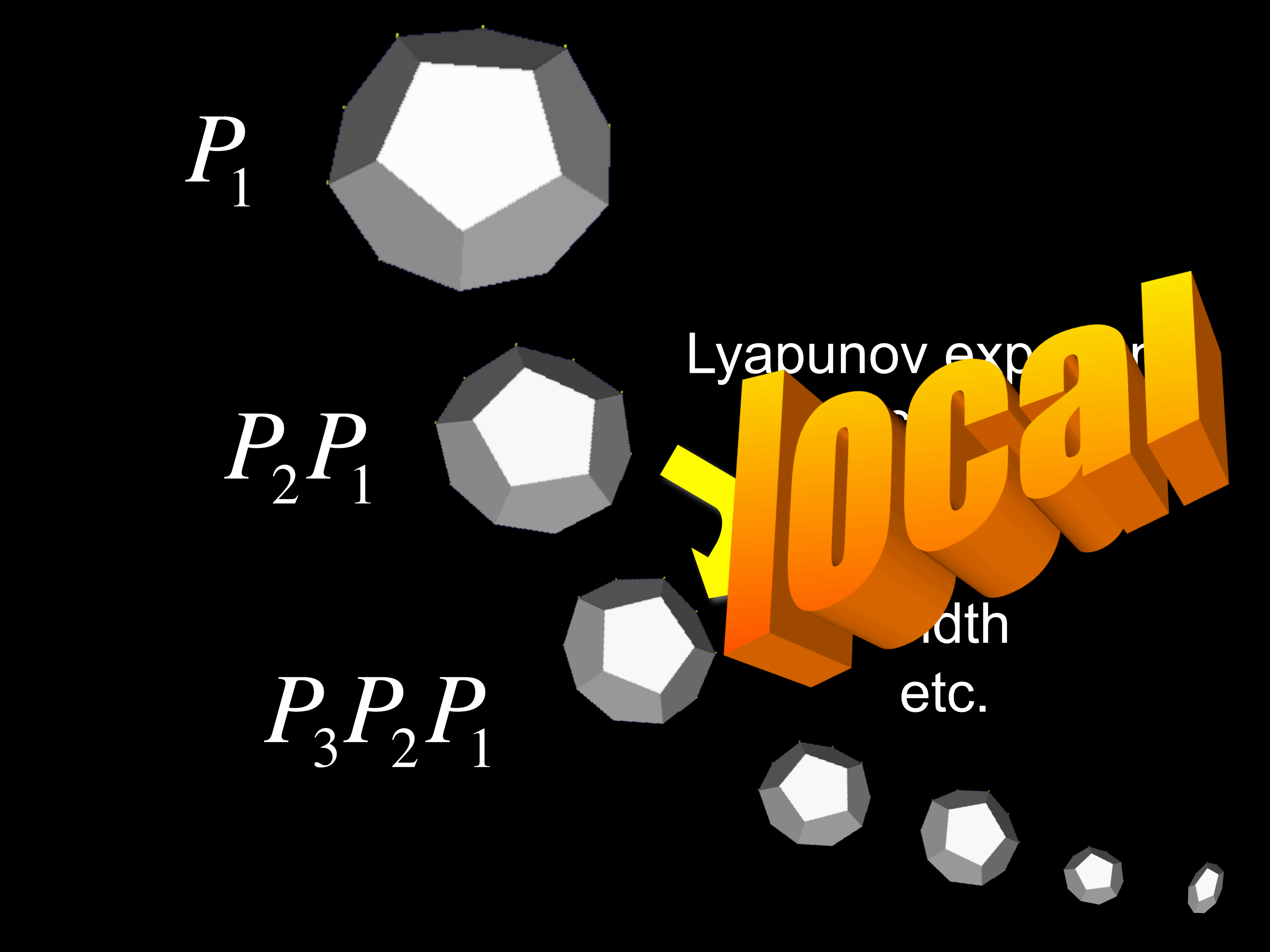
$P_2 \rightarrow$

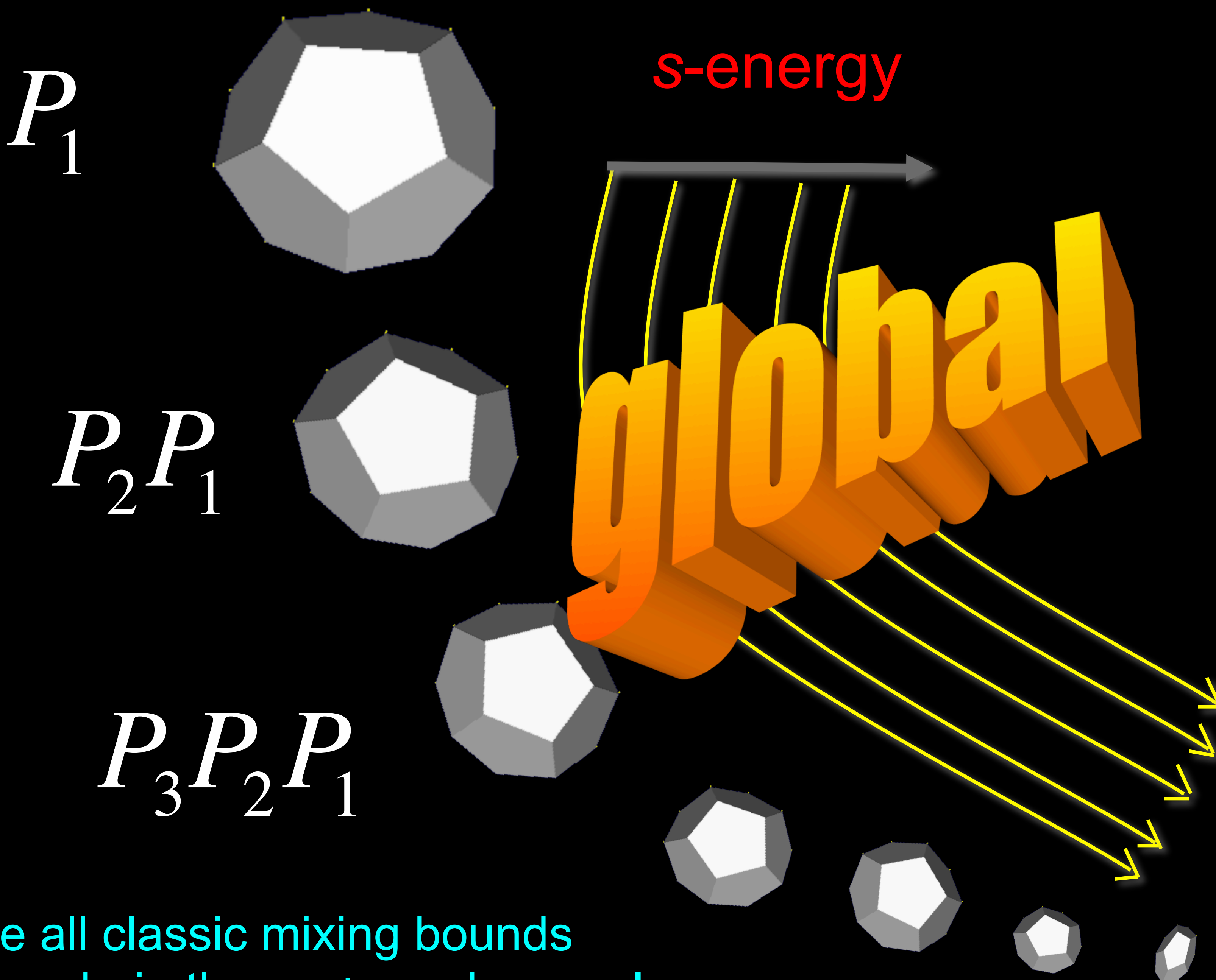
$P_1 \rightarrow$

$P_2 P_1 ?$

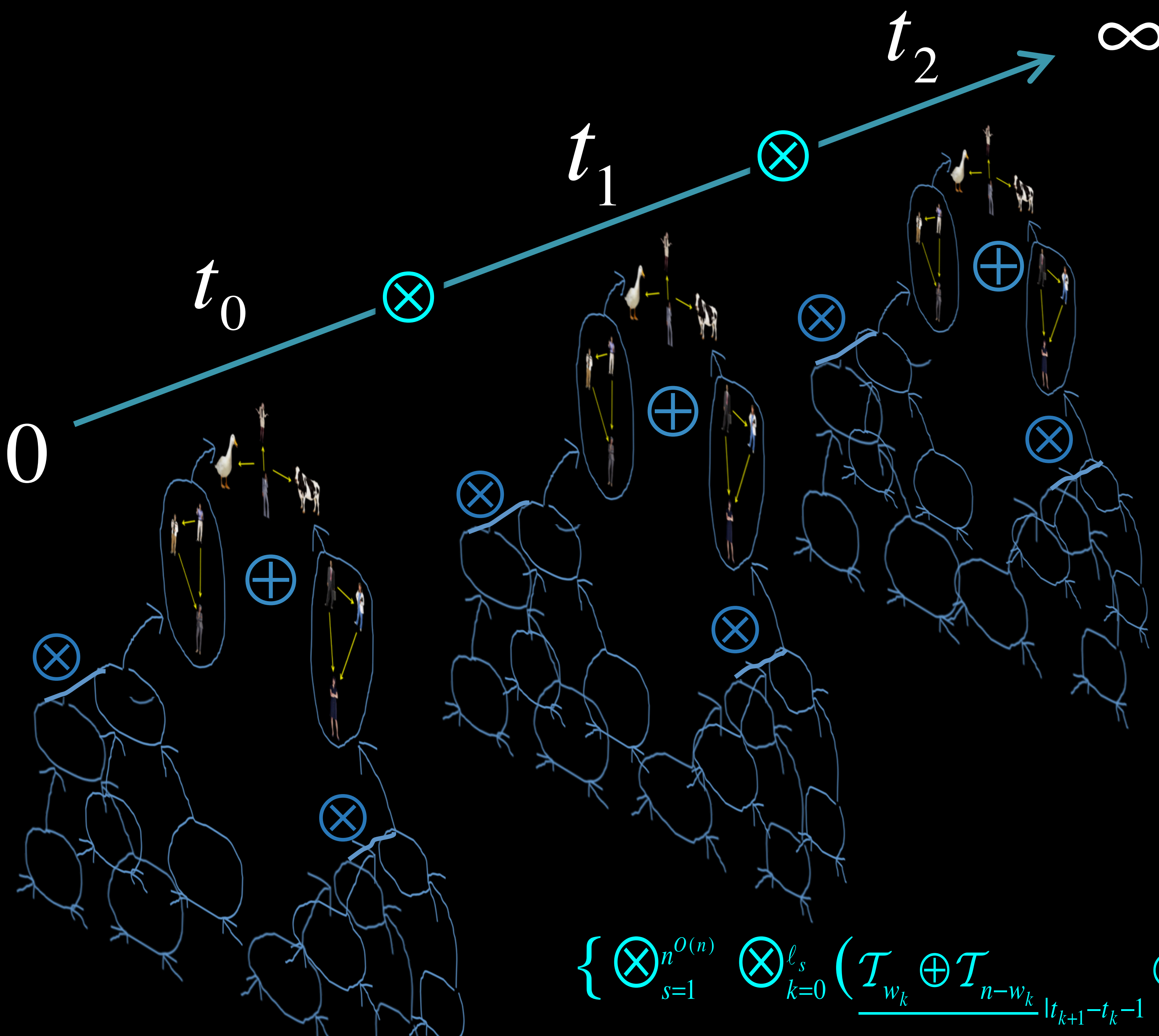
$P_2 \rightarrow$


$P_1 \rightarrow$
$P_2 P_1$?
$P_2 \rightarrow$

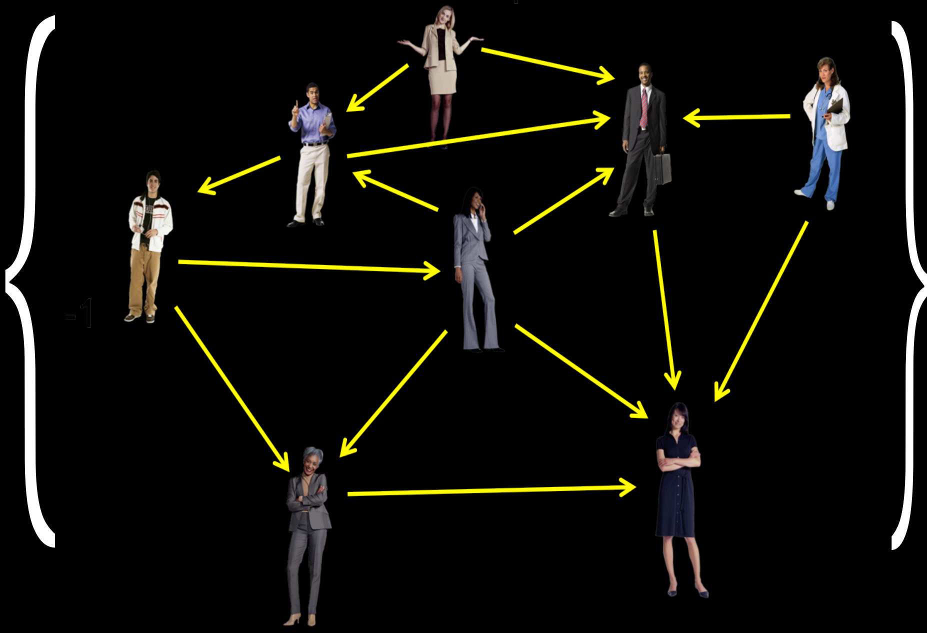

P_1
P_2P_1
$P_3P_2P_1$
Lyapunov exp
idth
etc.
local



Rederive all classic mixing bounds
in Markov chain theory + much more !

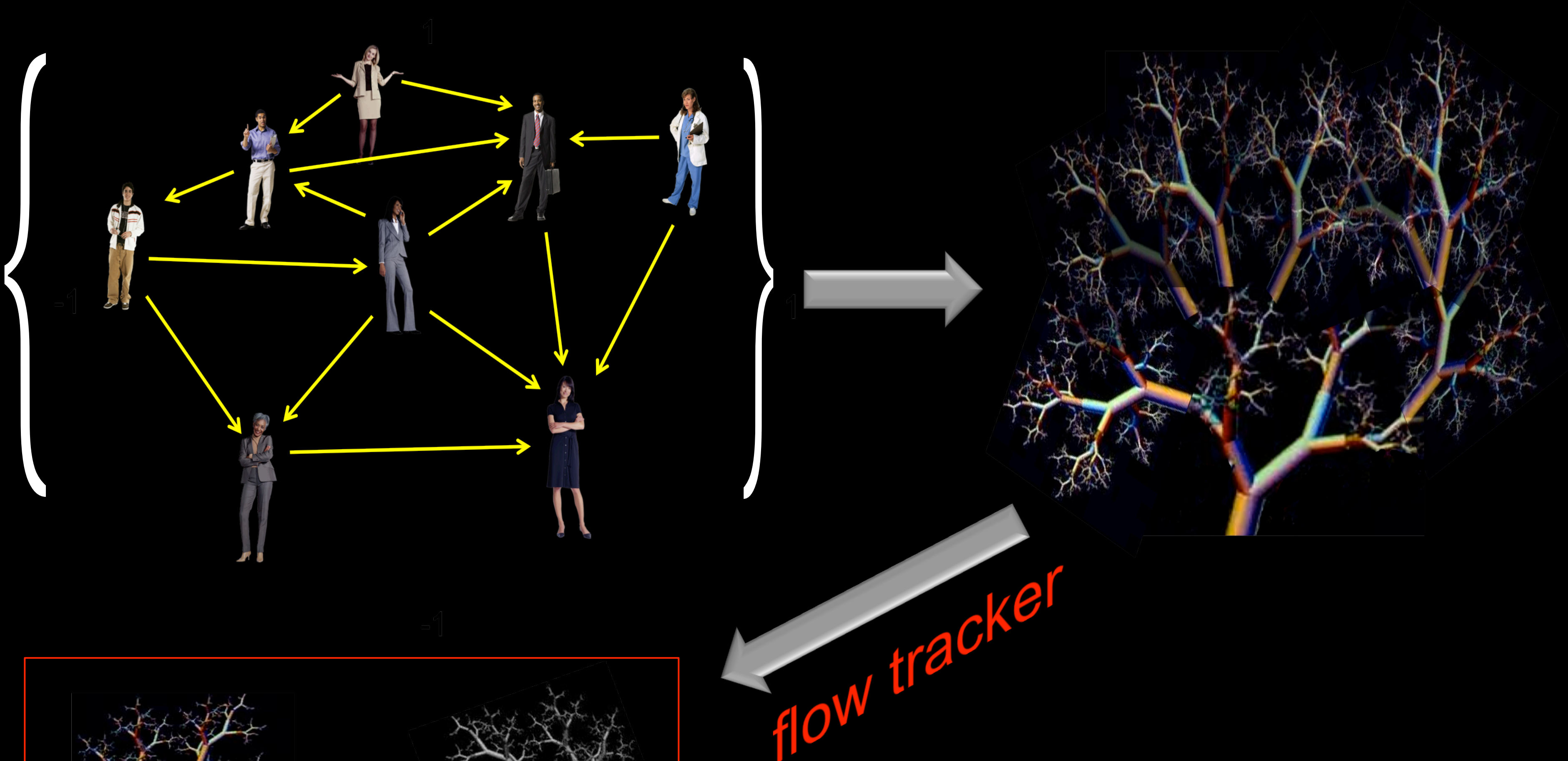


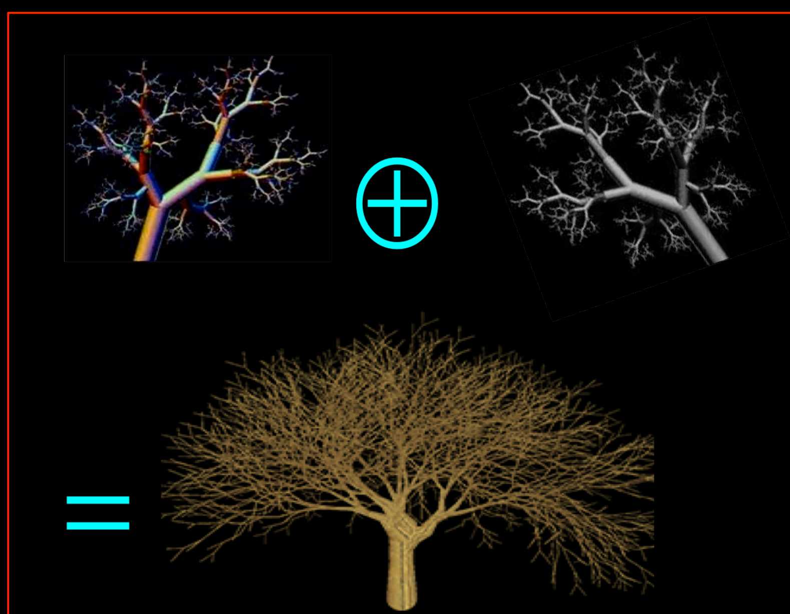
$$\left\{ \bigotimes_{s=1}^{n^{O(n)}} \bigotimes_{k=0}^{\ell_s} \left(\underline{\mathcal{T}_{w_k} \oplus \mathcal{T}_{n-w_k}}_{|t_{k+1}-t_k-1} \otimes \mathcal{T}_n^{|1} \right) \right\} \otimes \mathcal{T}_n^{*}$$



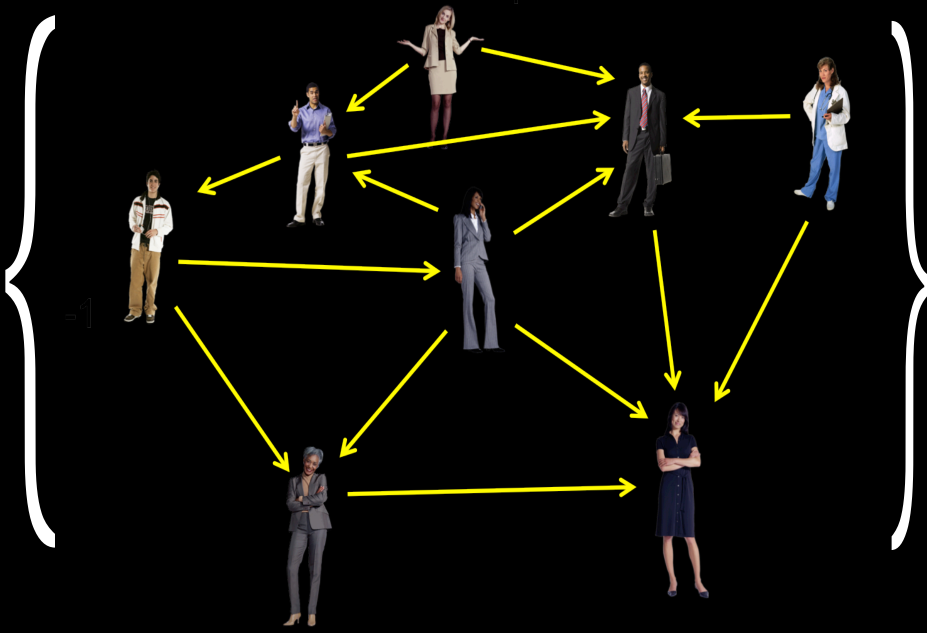
flow tracker

$$\left\{ \bigotimes_{s=1}^{n^{O(n)}} \bigotimes_{k=0}^{\ell_s} \left(\underline{\mathcal{T}_{w_k} \oplus \mathcal{T}_{n-w_k}}_{|t_{k+1}-t_k-1} \otimes \mathcal{T}_n^{\|1} \right) \right\} \otimes \mathcal{T}_n^{*}$$



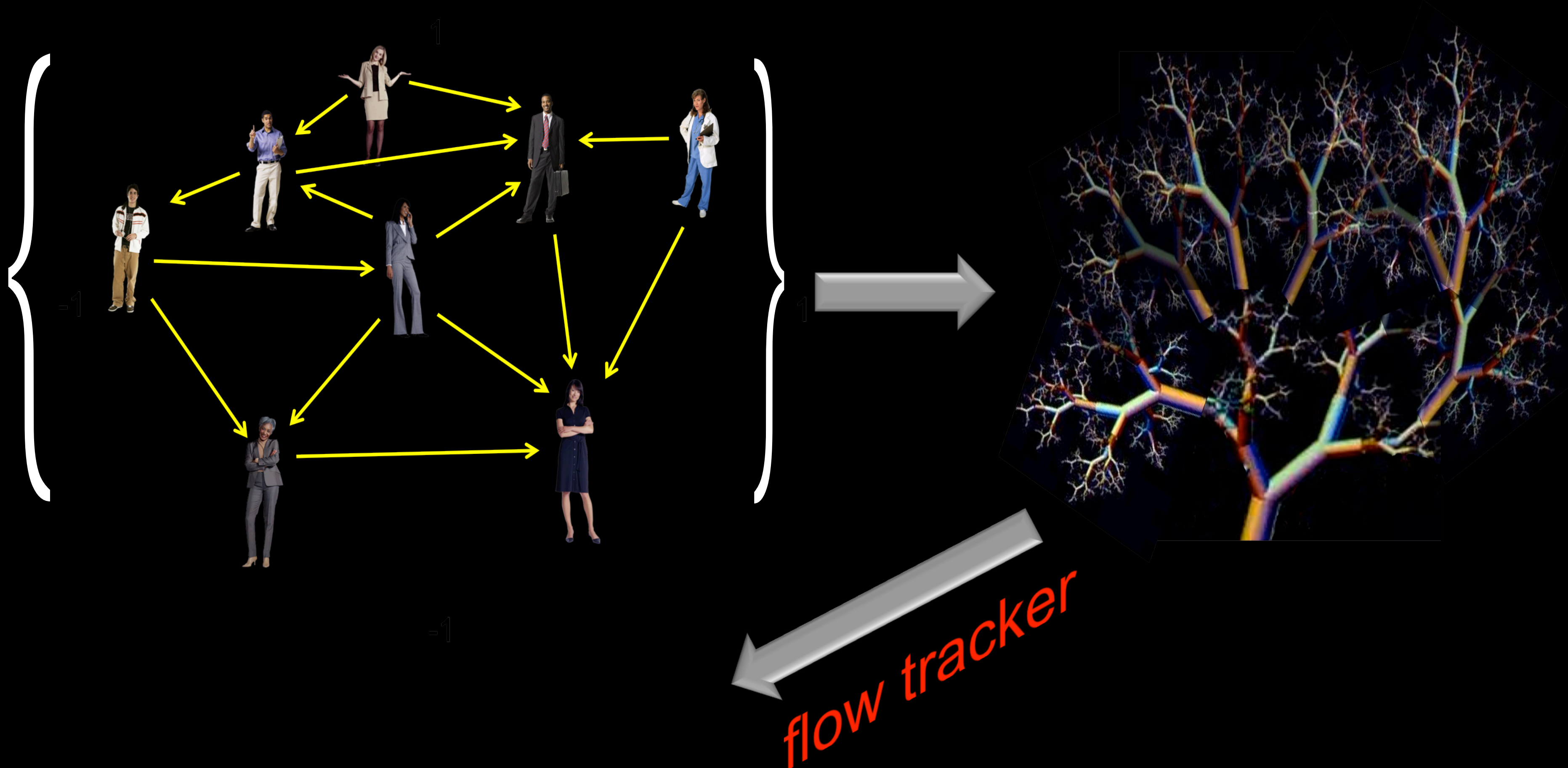


What the direct sum does



flow tracker

What the direct product does



$$\left\{ \bigotimes_{s=1}^{n^{O(n)}} \bigotimes_{k=0}^{\ell_s} \left(\underline{\mathcal{T}_{w_k} \oplus \mathcal{T}_{n-w_k}}_{|t_{k+1}-t_k-1} \otimes \mathcal{T}_n^{\|1} \right) \right\} \otimes \mathcal{T}_n^{*}$$

Bound entropy growth and energy decay term by term

If energy decays faster than entropy grows

then system is asymptotically periodic

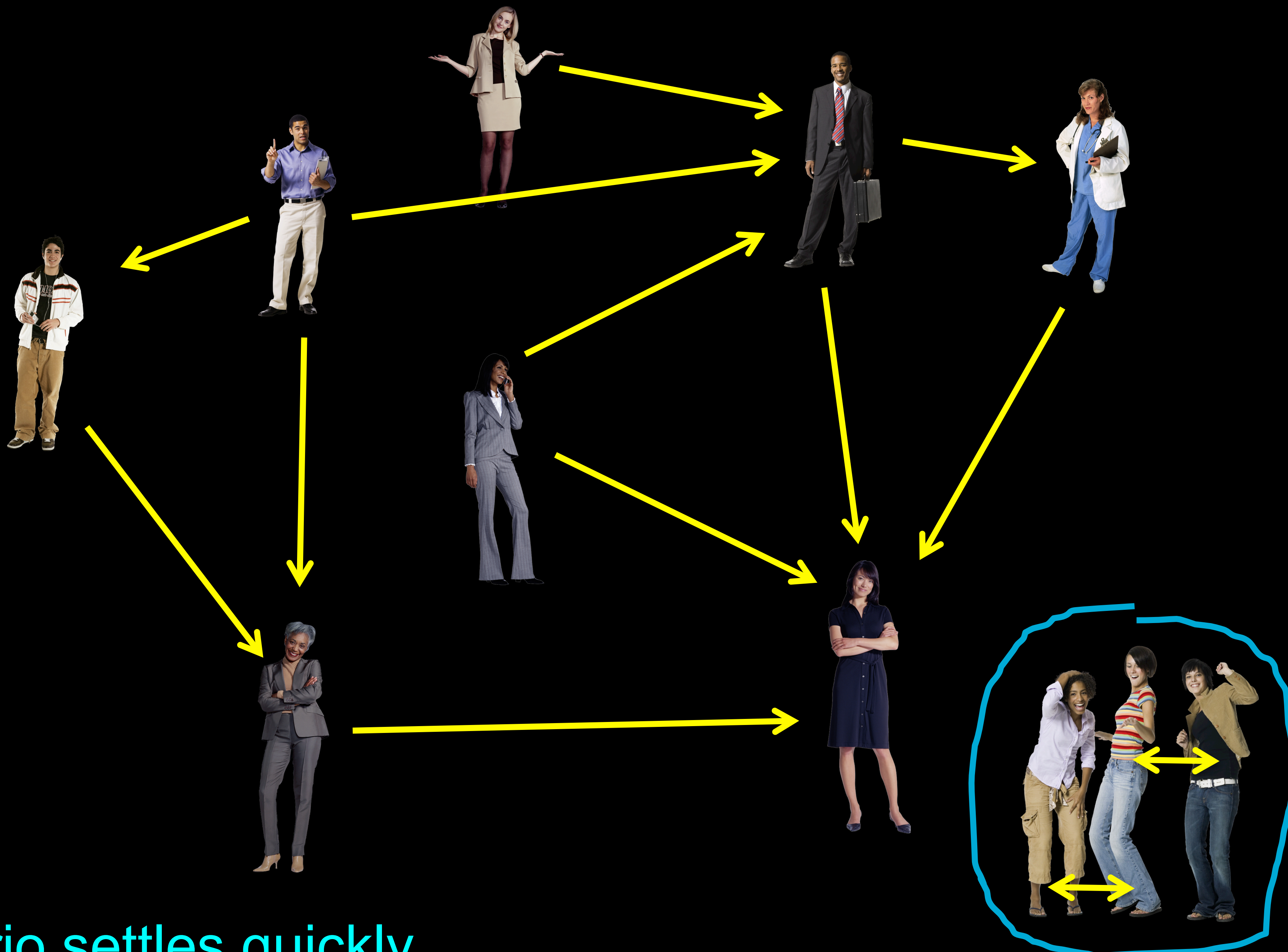
Theorem [C'12]

Diffusive influence systems are asymptotically periodic almost surely. They can be chaotic or even Turing-complete. Bidirectional systems have fixed-point attractors.

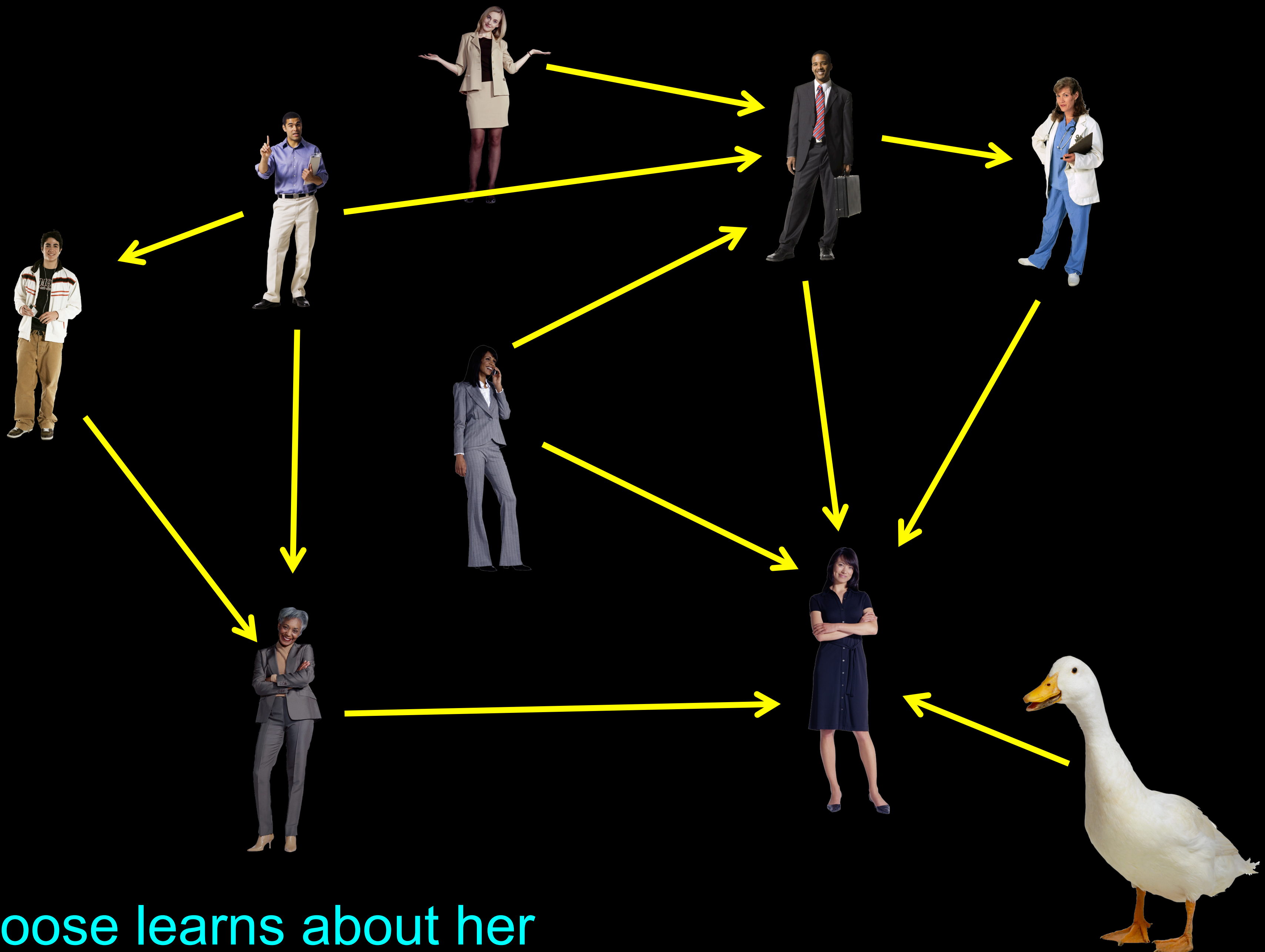
Number of attractors can be exponential (up to foliation)

The mixing of timescales creates

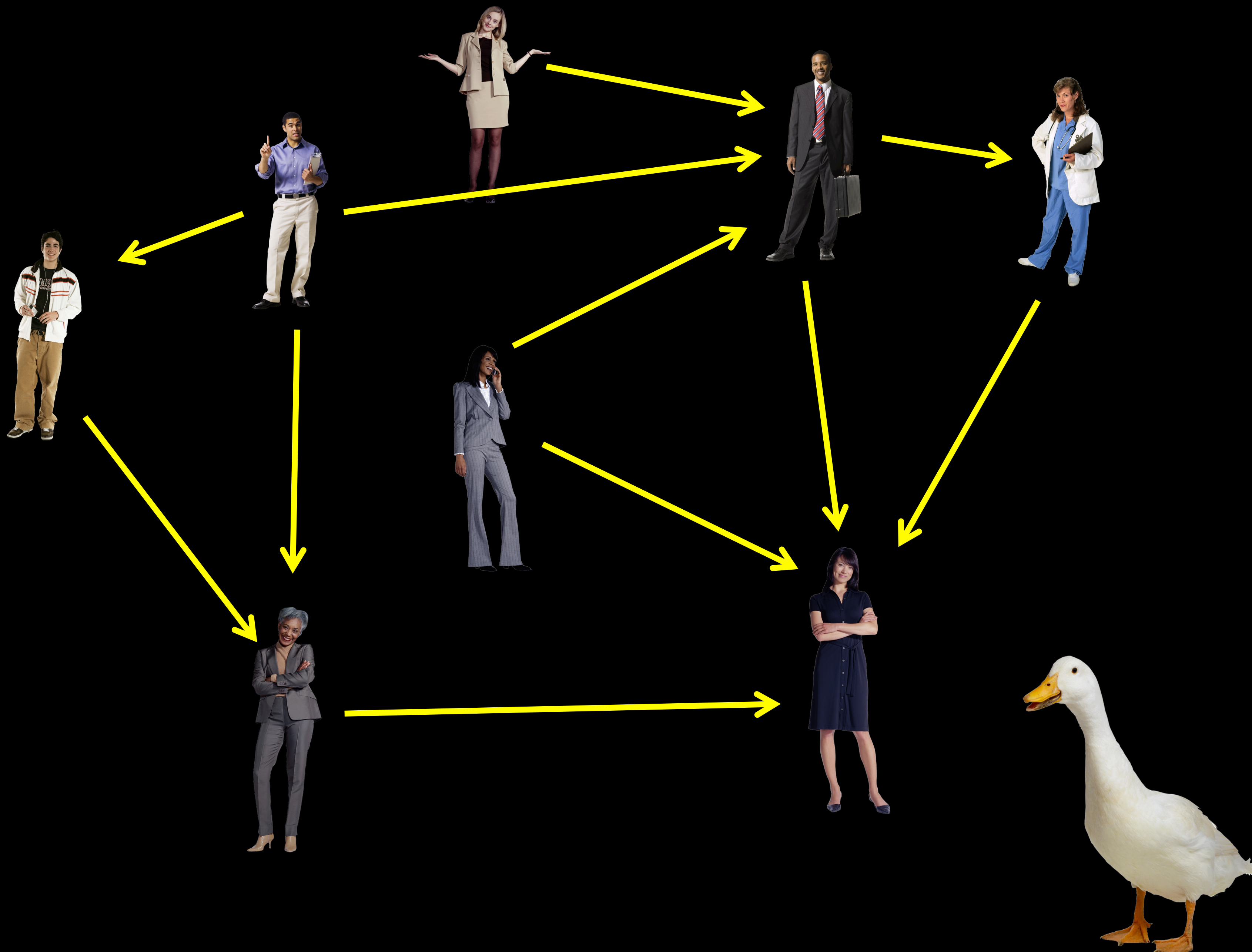
phenomena unknown in physics



Trio settles quickly



Goose learns about her



Limit cycle means amnesia

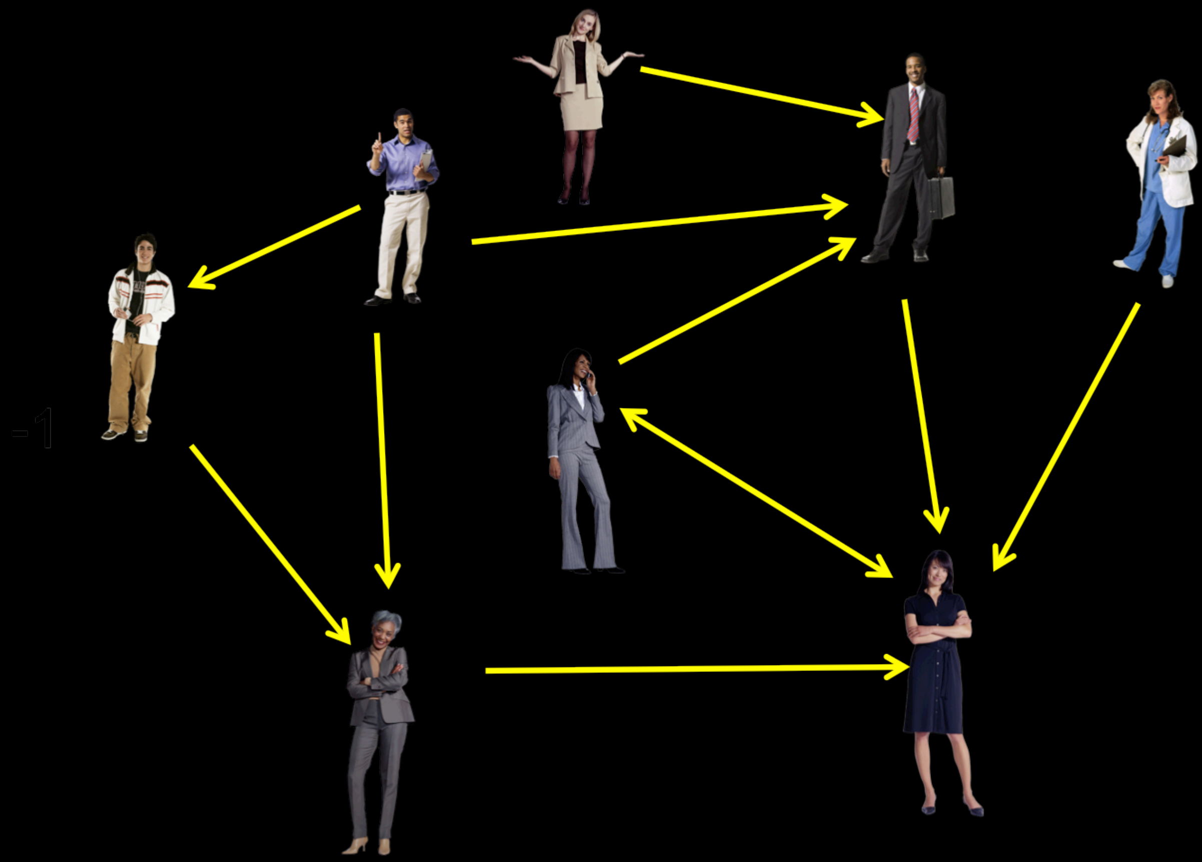
Shheitregyaleasshdeestroyedy!

Recurrent mixing of timescales

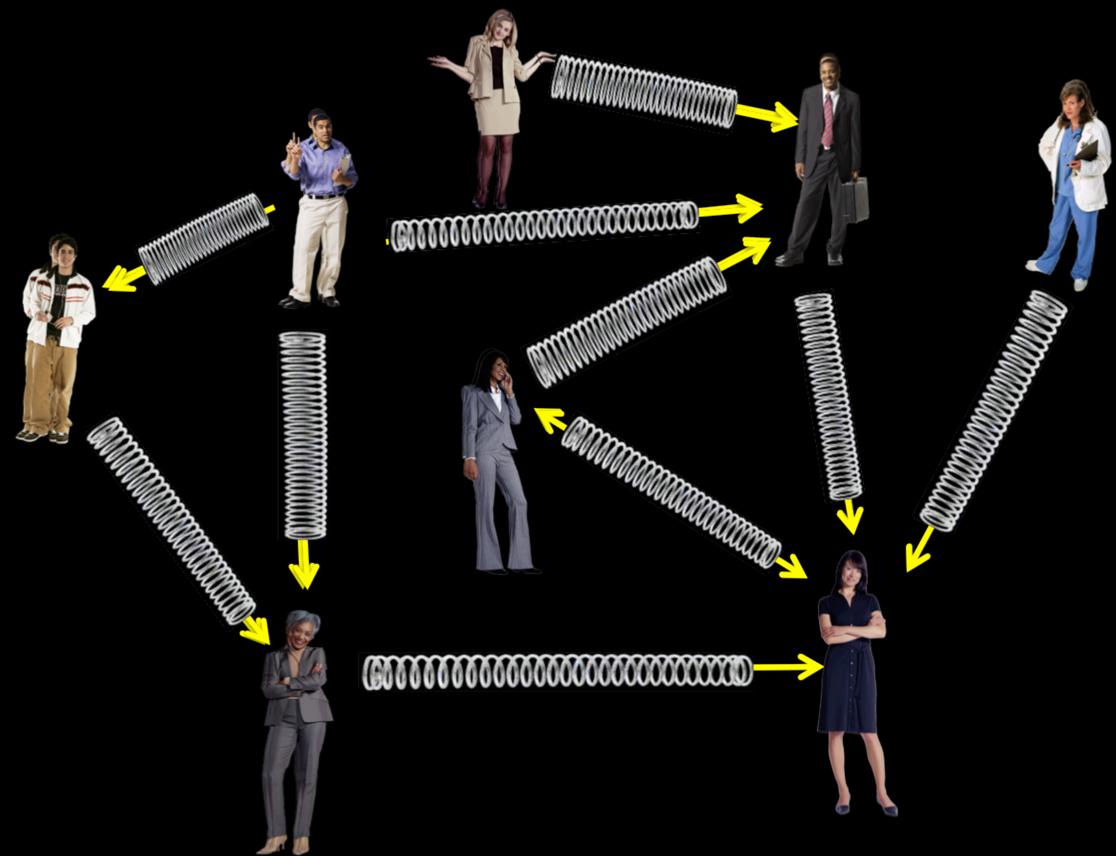
↓

Chaos and Turing universality

The view from physics

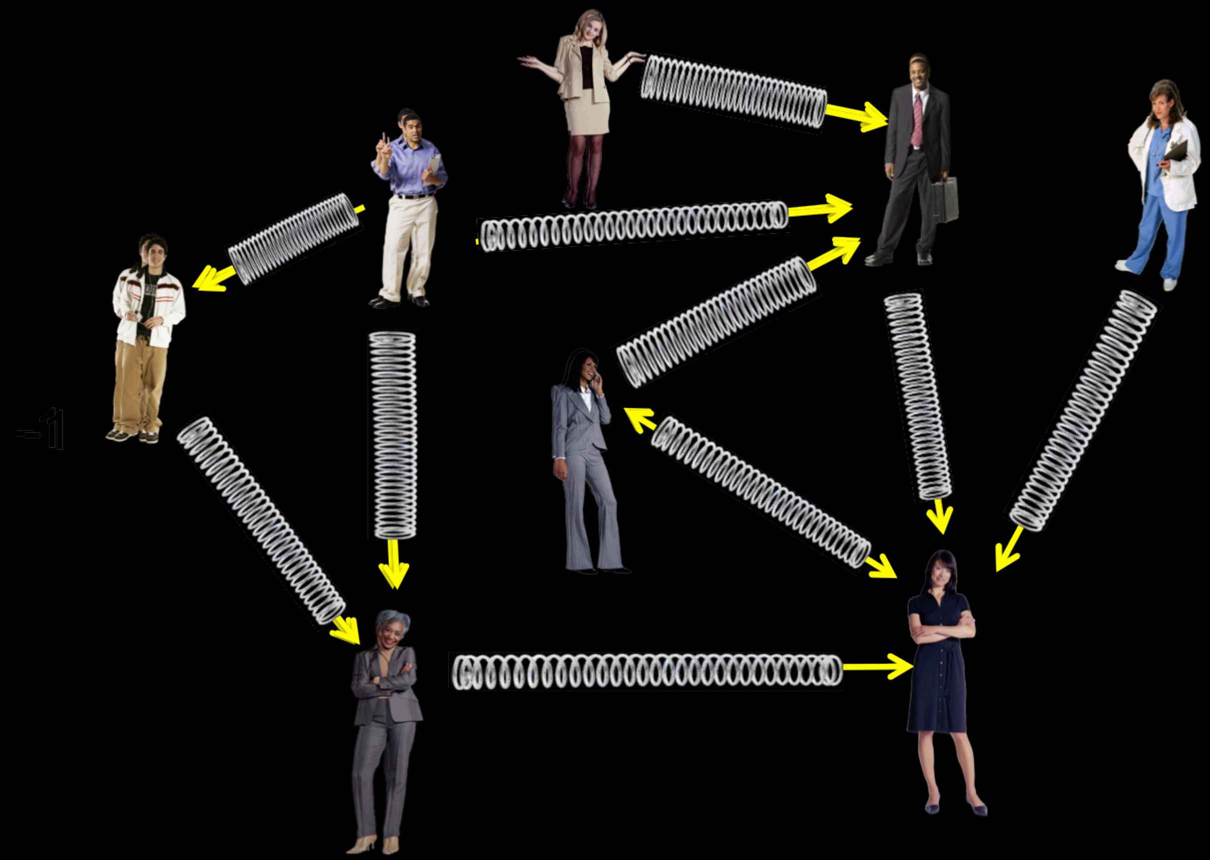


The view from physics



1-way springs with friction and changing topology

The view from physics

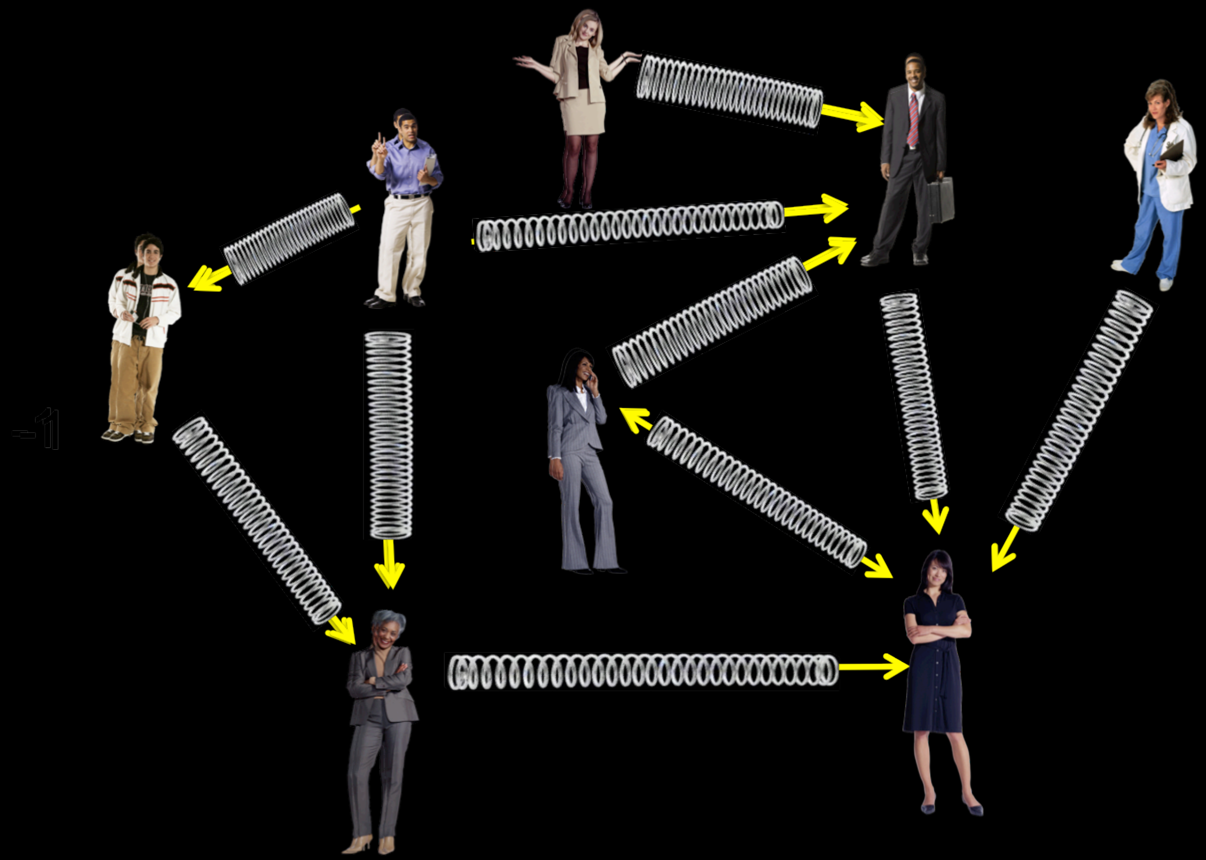


1-way springs with friction

Damped coupled oscillators

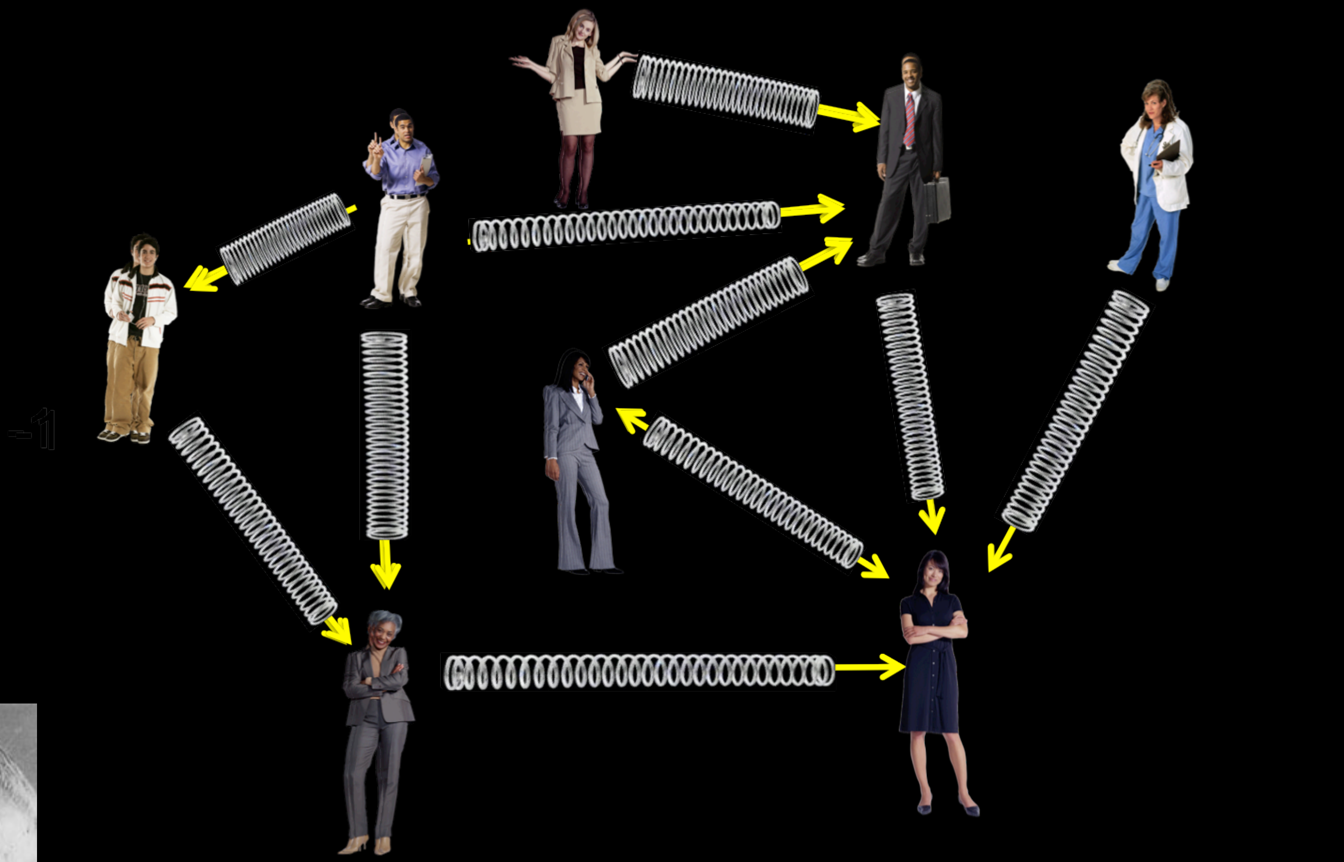
Minimize free energy

The view from physics



Changing topology re-injects free energy

The view from physics



Prigogine's *dissipative structures*

Capture the narrative complexity of natural algorithms

- Mixed scales via dynamic renormalization and influence systems
- Open systems
- Adaptiveness

(ongoing w/ Stan Leibler)