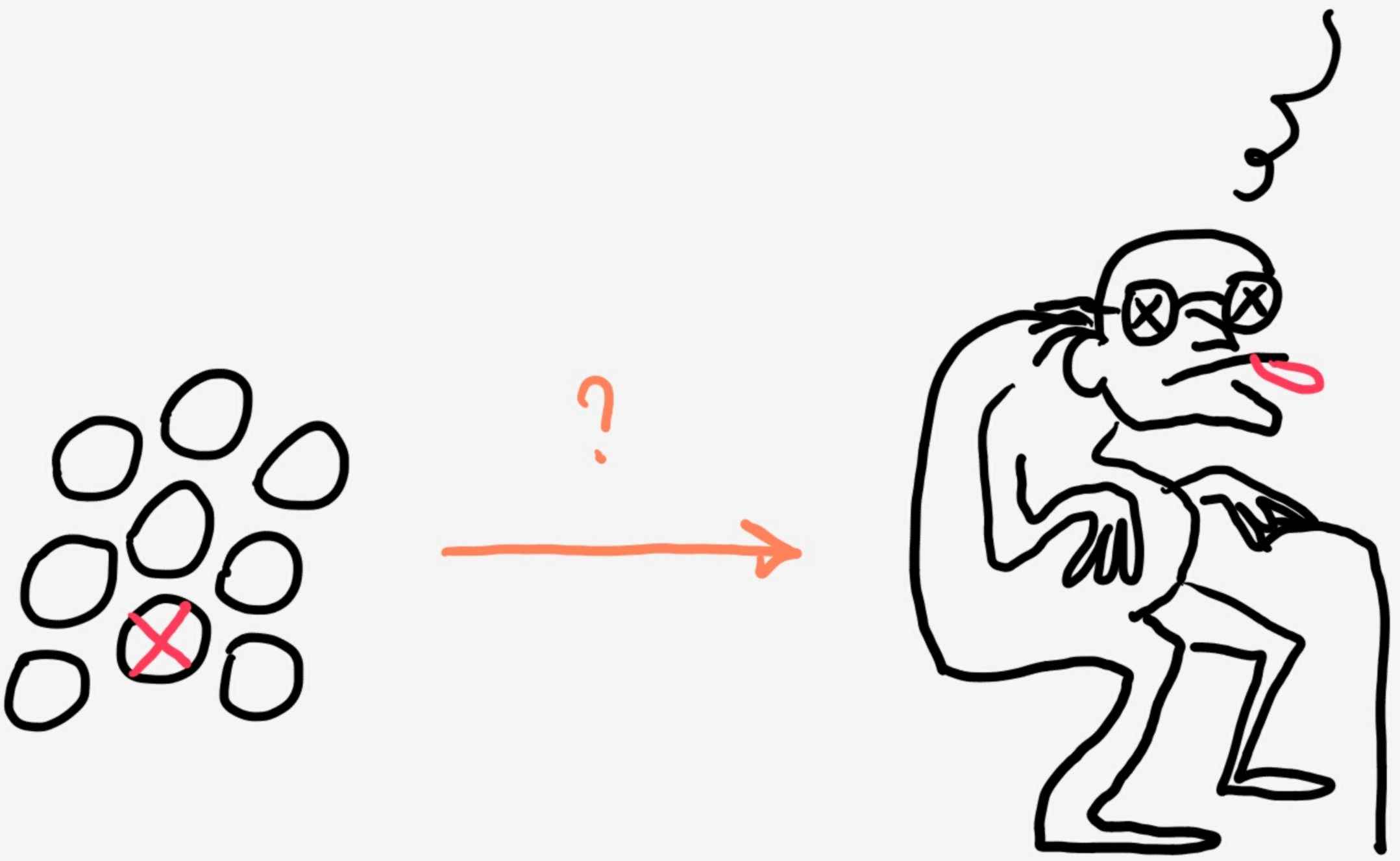
WHAT GOES ON BETWEEN CELL DAMAGE AND ORGANISM DEATH ?



Dervis Can Vural*

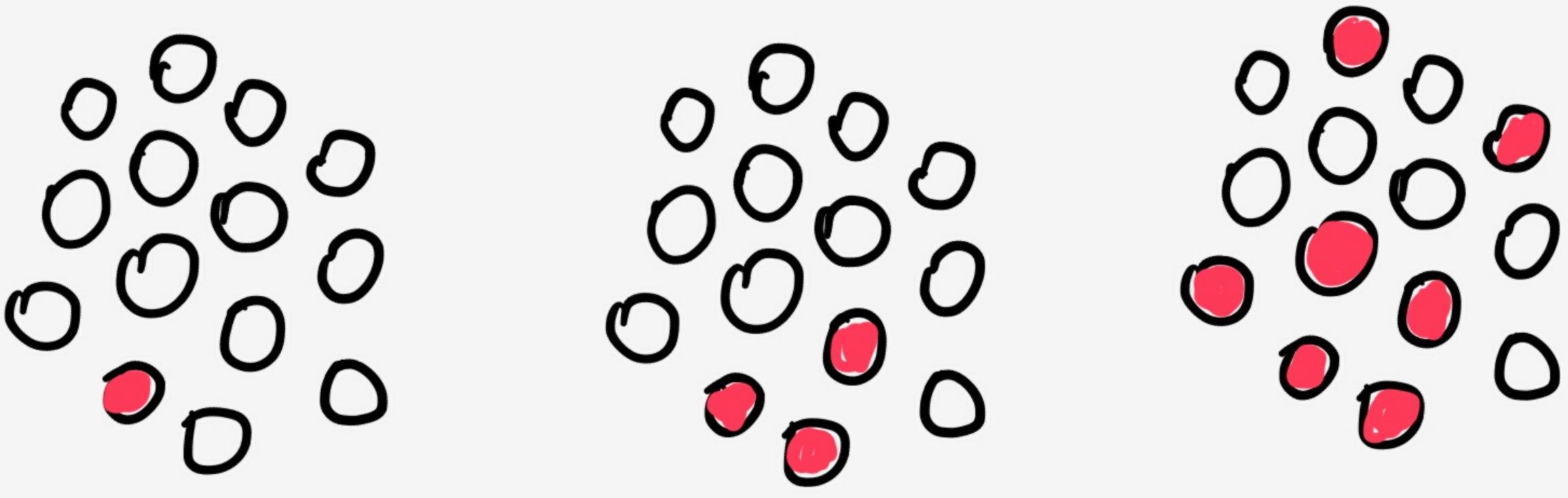
Daniel Suma

Pinar Zorlutuna

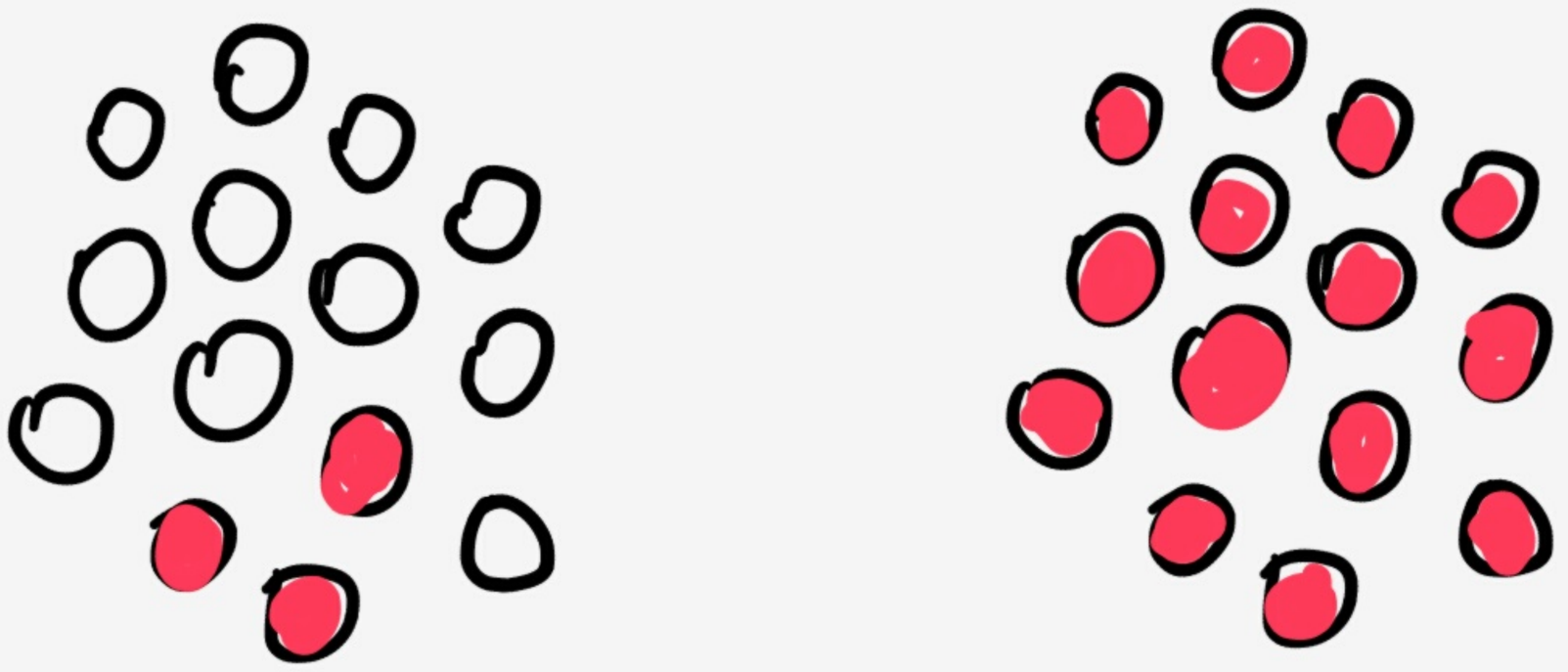
UNIVERSITY OF NOTRE DAME

AGING: QUALITATIVE CHARACTERISTICS

1. Failures are Accumulative



2. Catastrophic End.



Mechanistic Theories of Aging Focus on Cellular Processes.

Telomeres Shorten

Reactive Oxygen Species

- DNA Damage
- Protein Damage
- ⋮

CELLULAR THEORIES:

TRUE BUT SUPERFICIAL.

1. There are non-living things that age

Buildings, Machines, Devices, Software Companies, Empires, Materials, ...

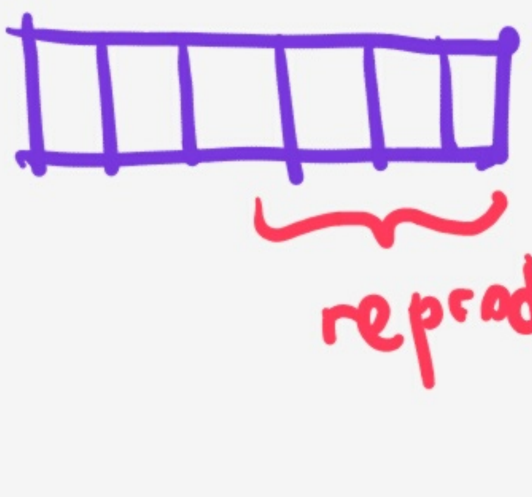
2. There are living things that do not age

3. The things that do age do so not because they run out of cells.

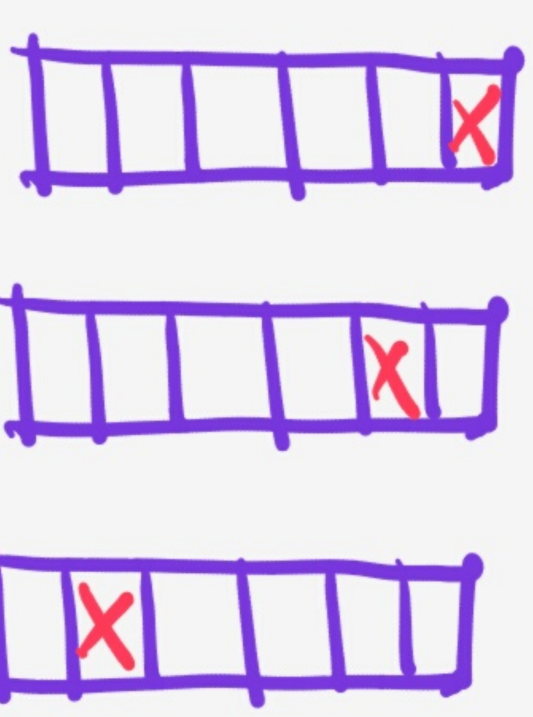
EVOLUTIONARY THEORIES:

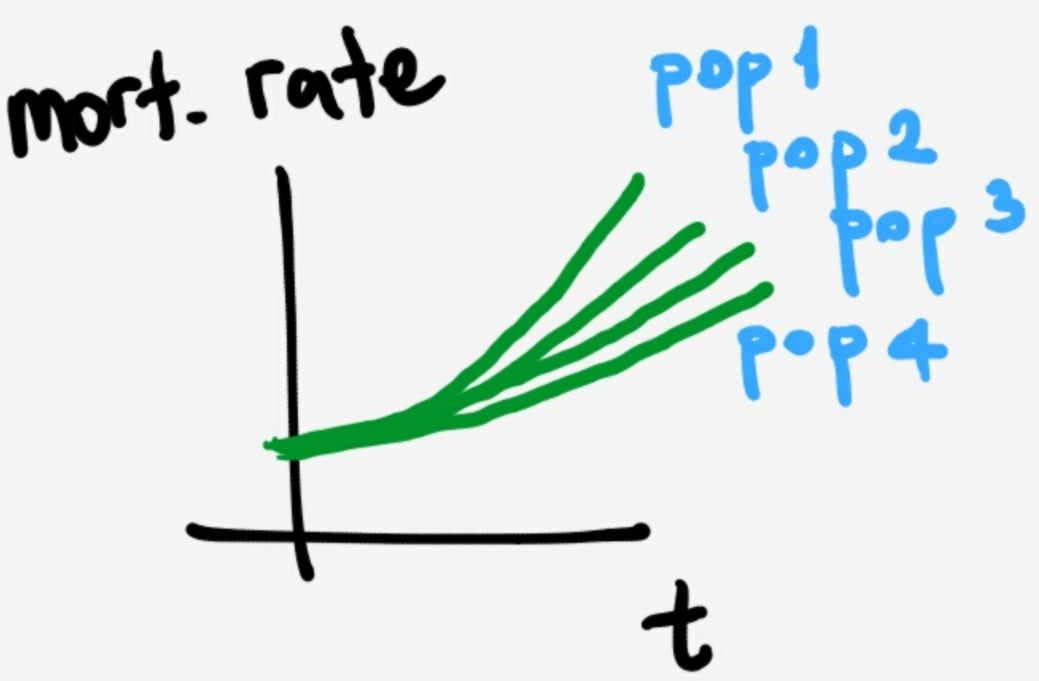
PROBABLY TRUE (BUT SOMETHING IS MISSING)

Life history



1 MUTATION ACCUMULATION





EMPIRICALLY UNTRUE

2 ANTAGONISTIC PLEIOTROPY

Lifespan-increasing mutations

decrease fecundity

EMPIRICALLY UNTRUE

OUR STORY:

- Aging is an emergent property of a system with highly interdependent components

- The microscopic cause of component failure is irrelevant

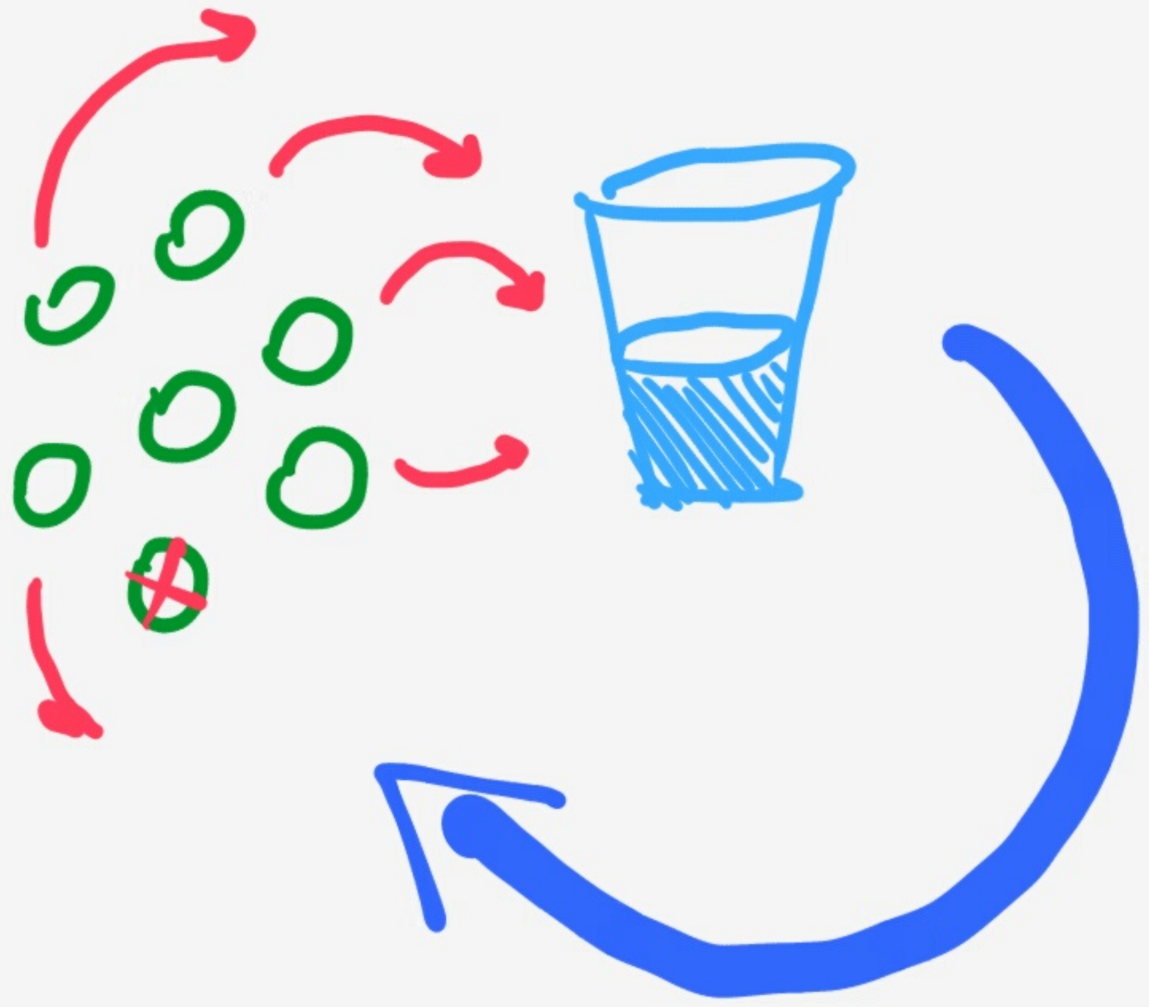
- The number of components and their interactions are relevant

EVOLUTIONARY + MECHANISTIC

THE EVOLUTION OF DEPENDENCE FORMATION

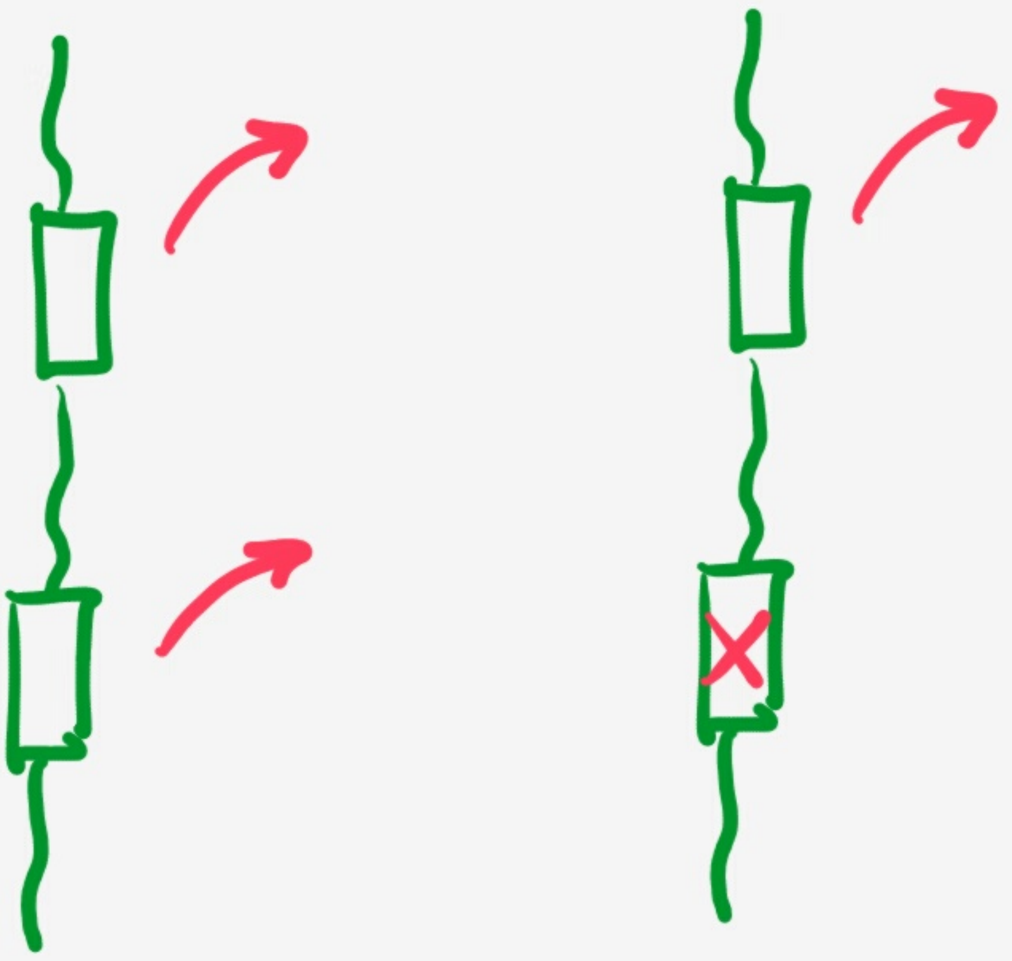
Example 1:

Collective Digestion



Example 2

Duplicate Genes

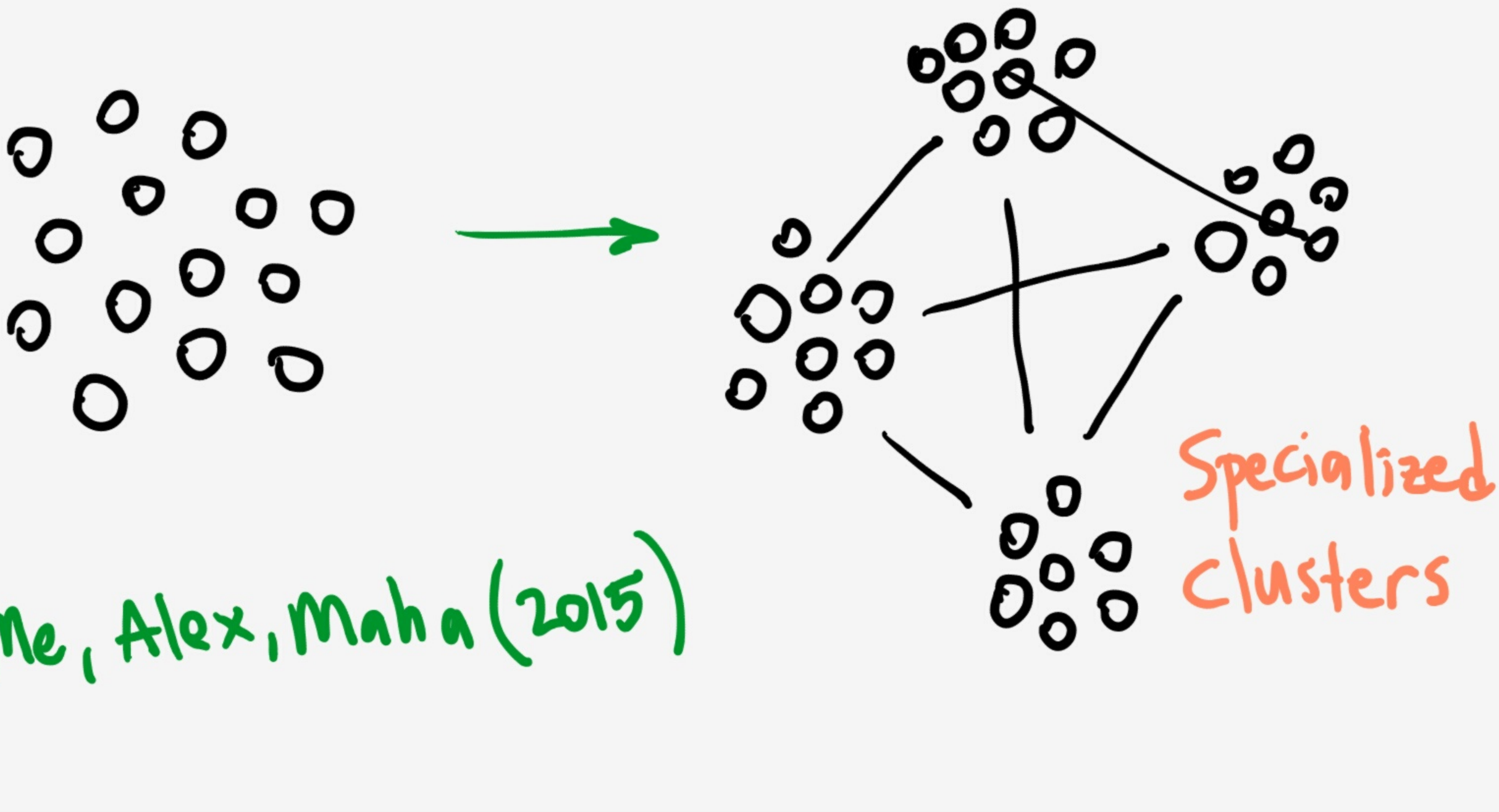


NEUTRAL EVOLUTION OF DEPENDENCE FORMATION

Me, Greg, Maha (2014)

Random Interdep Networks

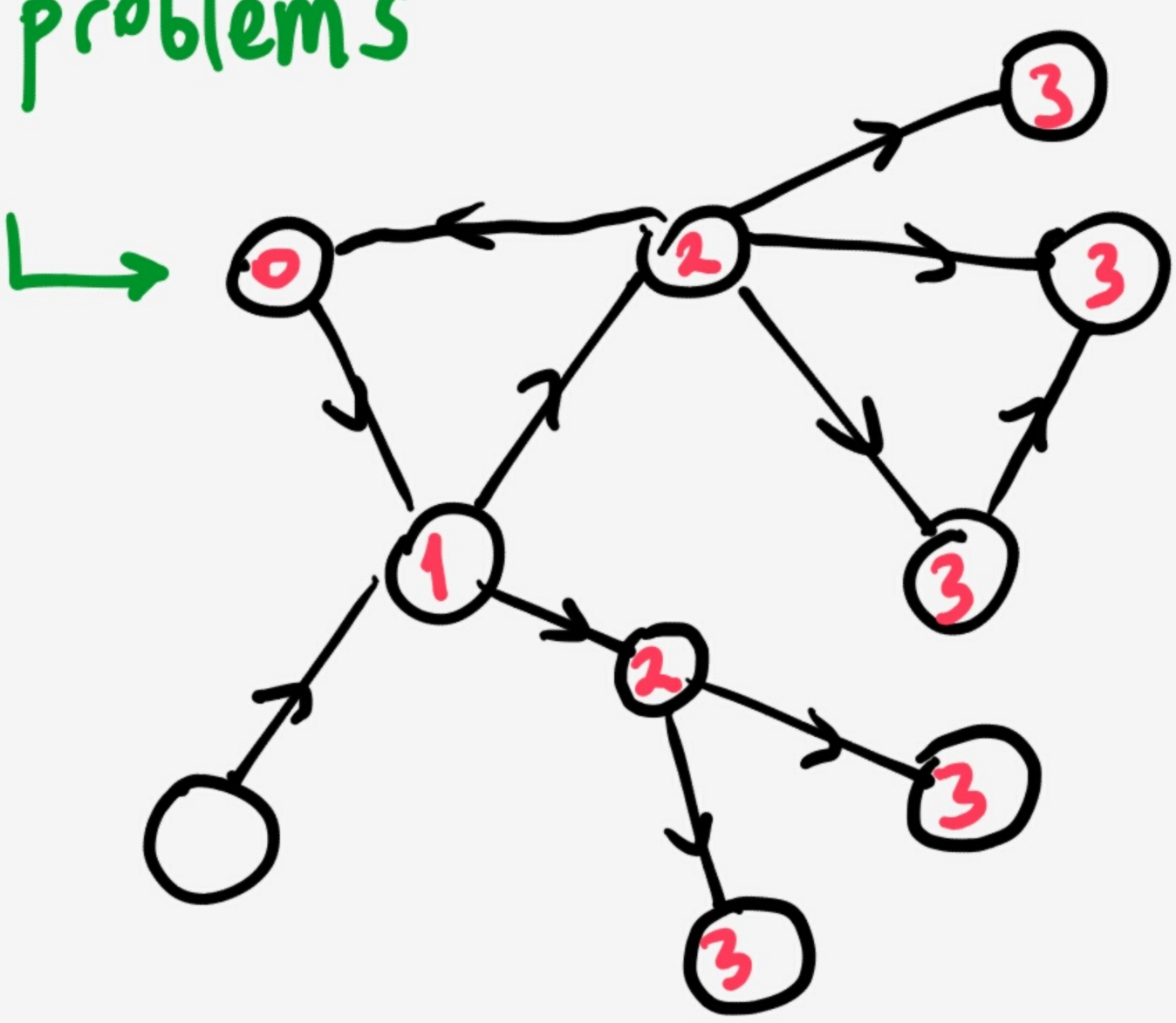
NON-NEUTRAL EVOLUTION OF DEPENDENCE FORMATION



Me, Alex, Maha (2015)

AGING: Propagation of Failure Through an Interdep Network

minor problems



cause catastrophic consequences

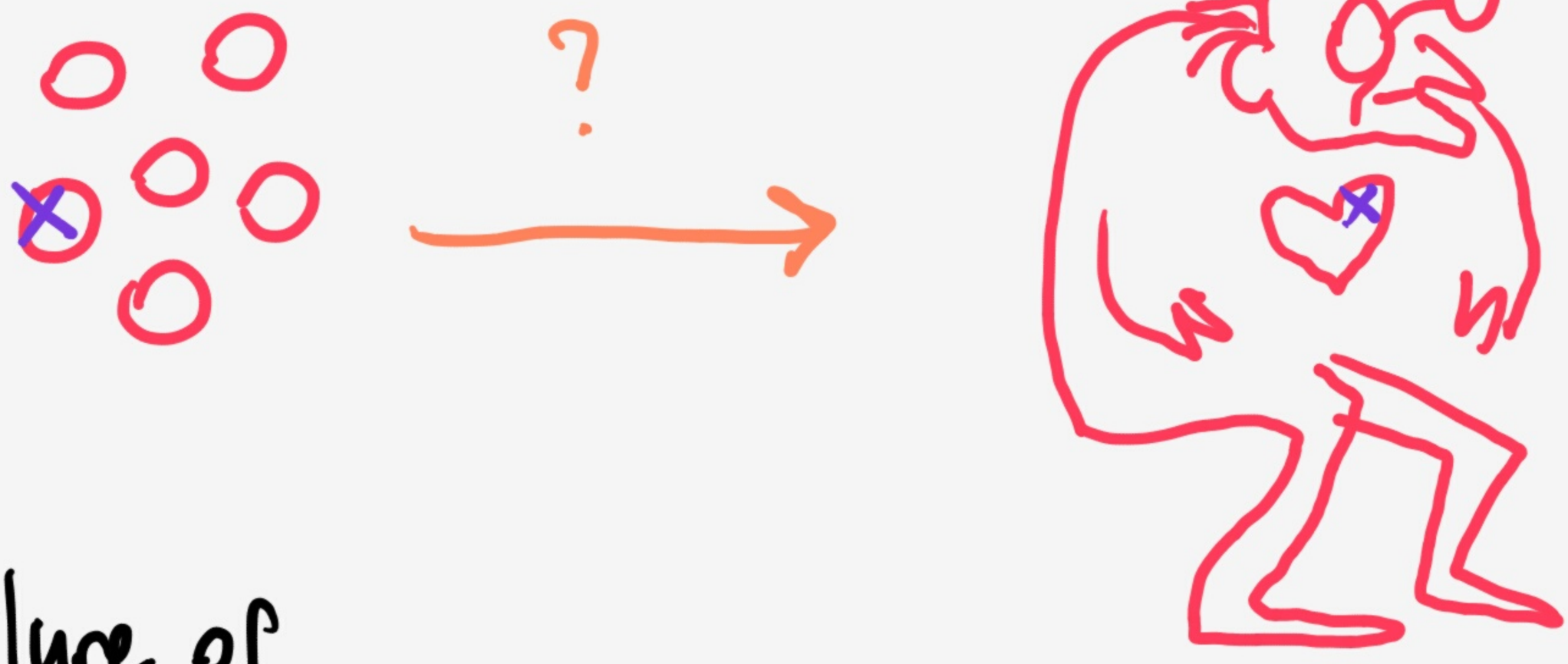
NICE IDEA, BUT:

- What is the network structure?

- What is the dynamic law that propagates failures?

ORGANISM: ??

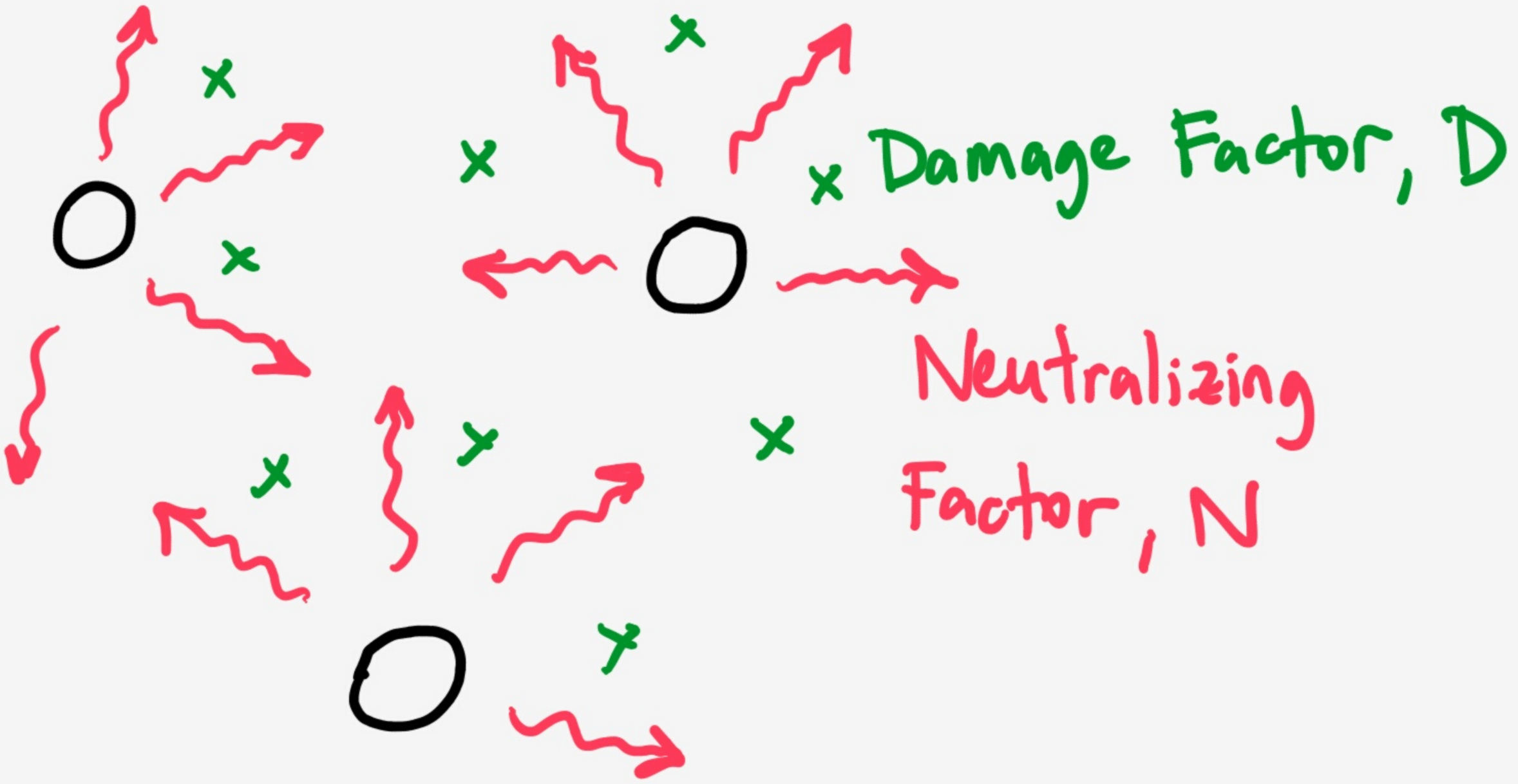
TISSUE: ✓



Failure of Cells

Failure of Organism

INTERDEPENDENCE STRUCTURE IN A TISSUE



Assumptions:

Diffusion Equation

$kN + D \longrightarrow$ O.K.

Prob. Alive $\propto$ [O.K.]

NUTS & BOLTS

DIFFUSION EQN

$$\frac{d\phi_i}{dt} = D\nabla^2\phi_i - k\phi_i + S(\vec{r} - \vec{r}_i)$$

position of cell i

diffusion decay source

REACTION KINETICS + INTRINSIC DEATH RATE

$$P_{death}(r_i) = \frac{\text{const.}\ \Phi_0^{\,k}}{\Phi(r_i)^k + \Phi_0^{\,k}} + \text{const.}$$

$$\Phi(r_i) = \int \phi(r_i - r)\, d^3r$$

threshold

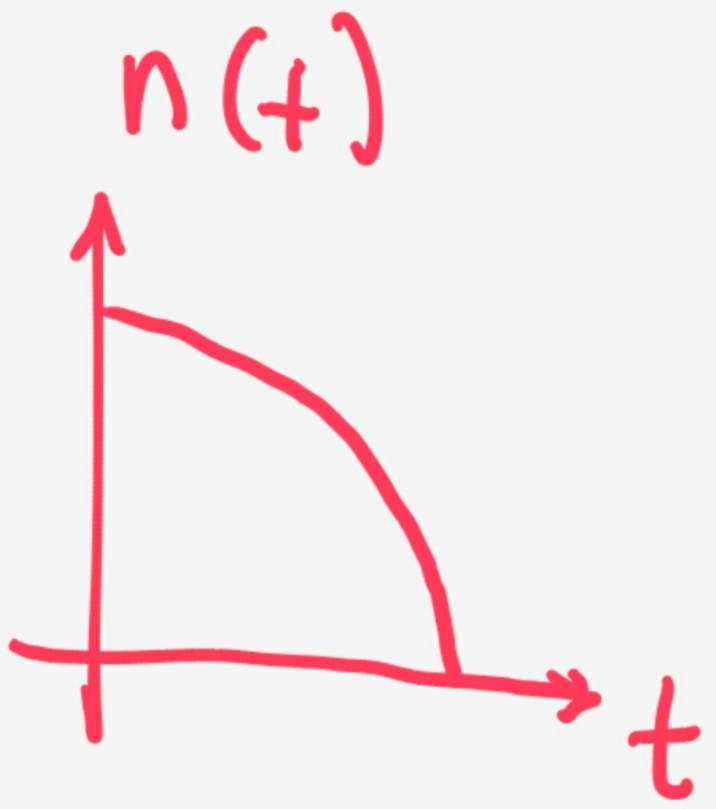
POPULATION DYNAMICS

$$\frac{dn}{dt} = -P_{death} \cdot n$$

Solve Everything

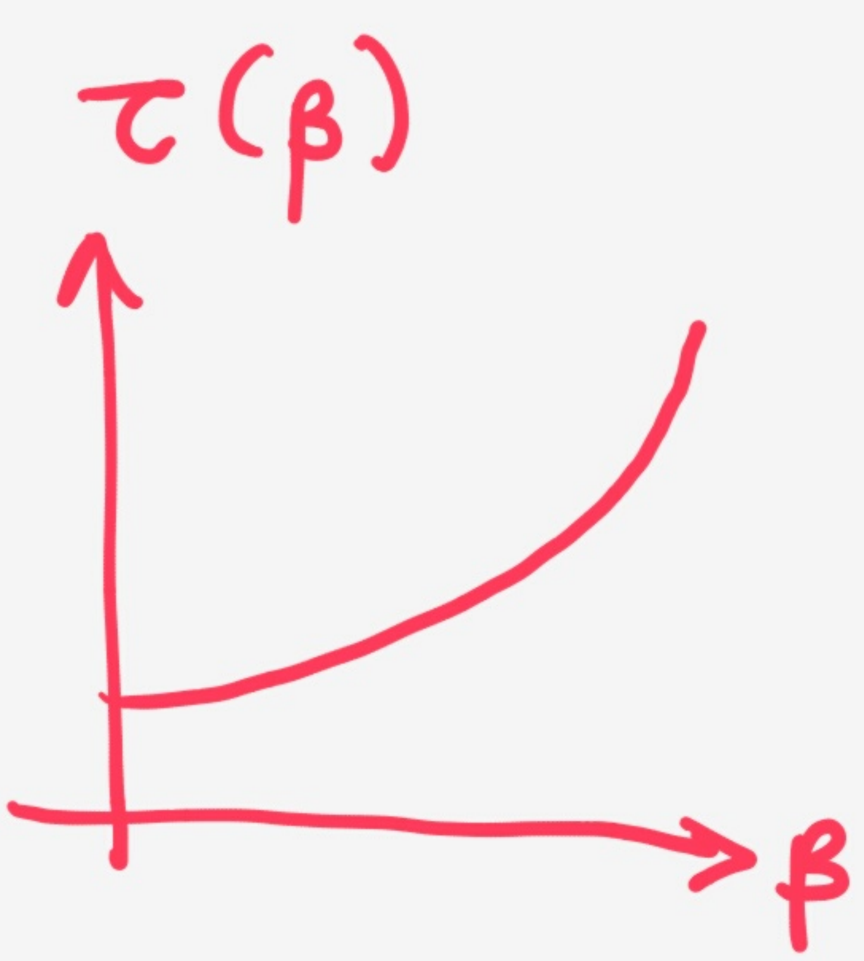
LIVE CELLS

$$n(t) \sim (B - ct)^{1/k}$$



LIFETIME

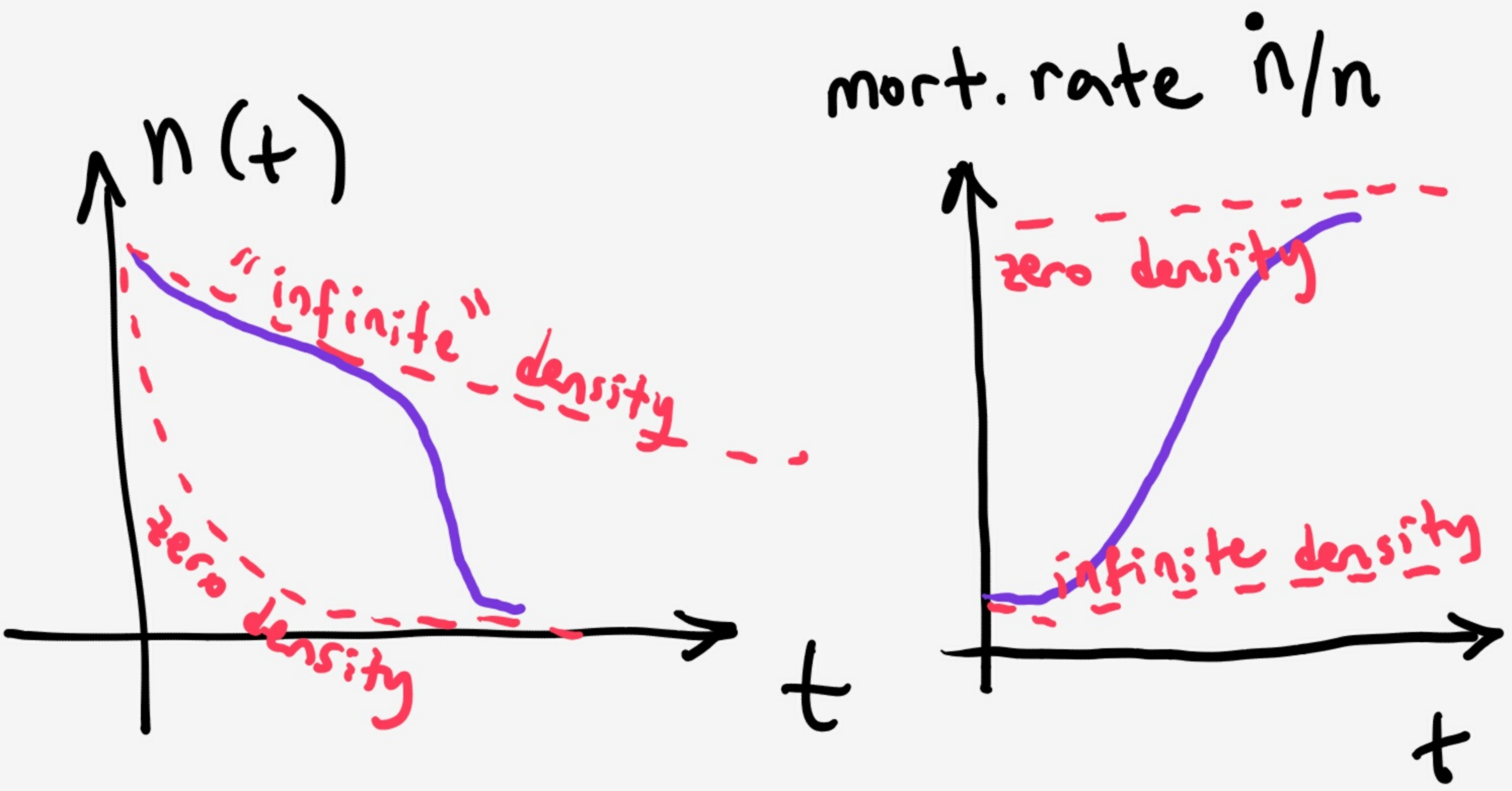
$$\tau = \frac{\beta^k + k \log \beta}{\alpha k}$$



$$\beta = \frac{(\text{sec. rate})(\text{init. pop.})(\text{decay len.})^2}{(\text{diff const})(\text{threshold } \phi_0)}$$

Summary of Results

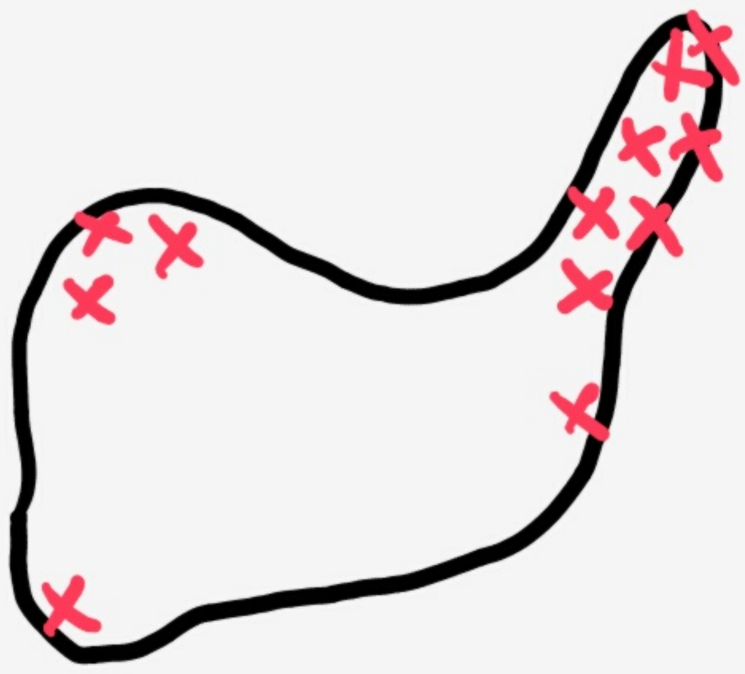
1. Catastrophic Collapse due to a transition between time scales



2. Boundary Effect:

Tissues Fail Inwards

3. Shape Matters. High Curvature Regions Fail First.



4. Complex Interplay between Boundaries & Bulk.