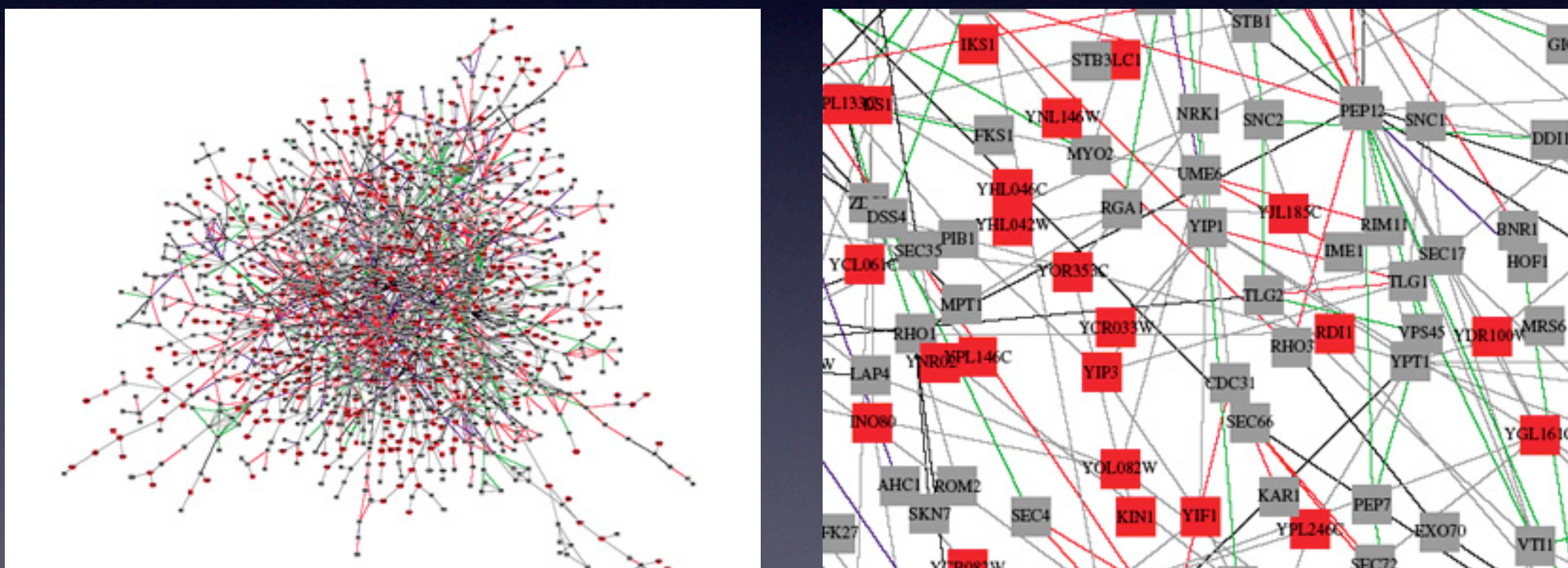
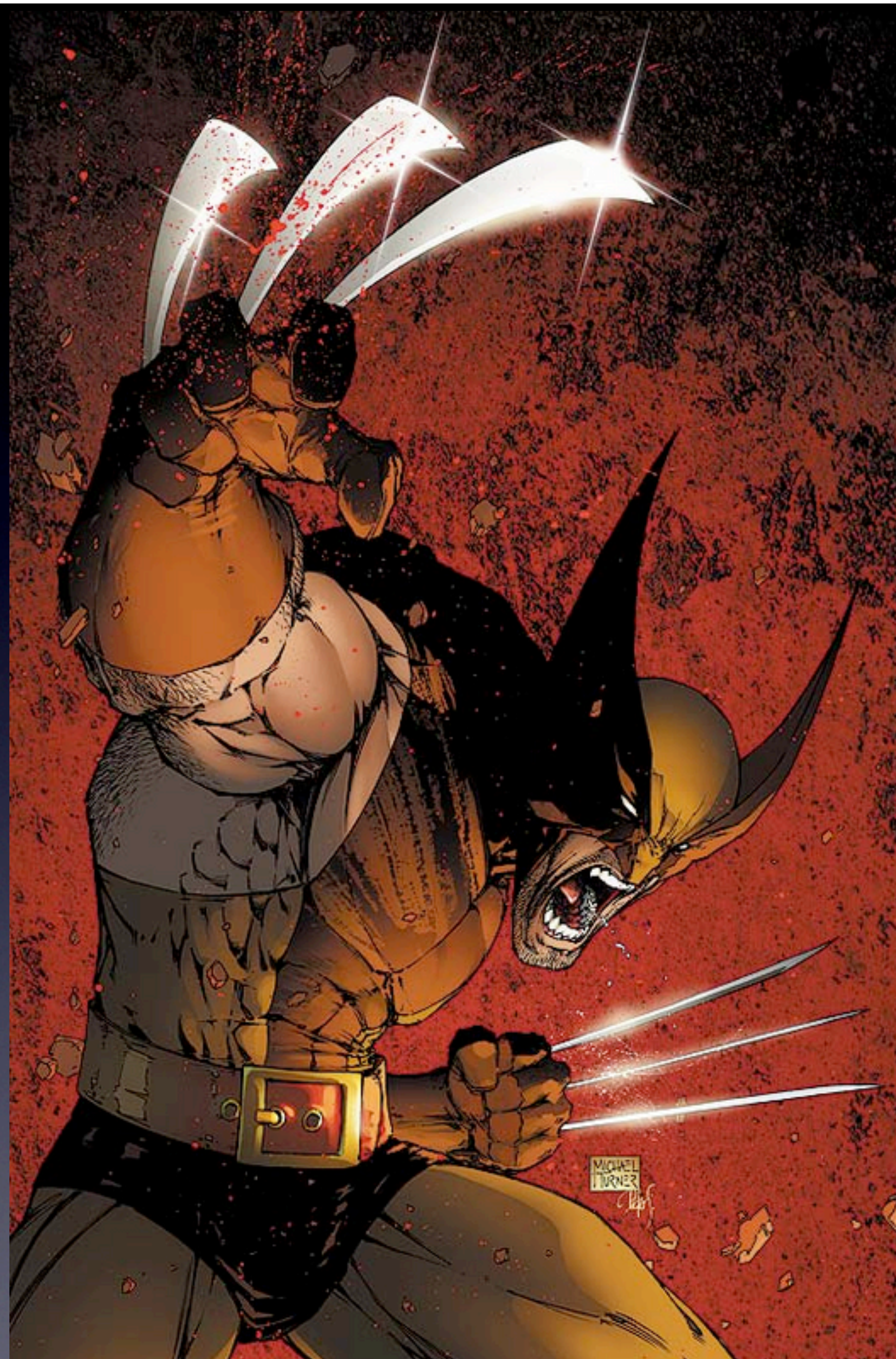
The Experimental Logic of Network Approaches to Robustness in Complex Systems

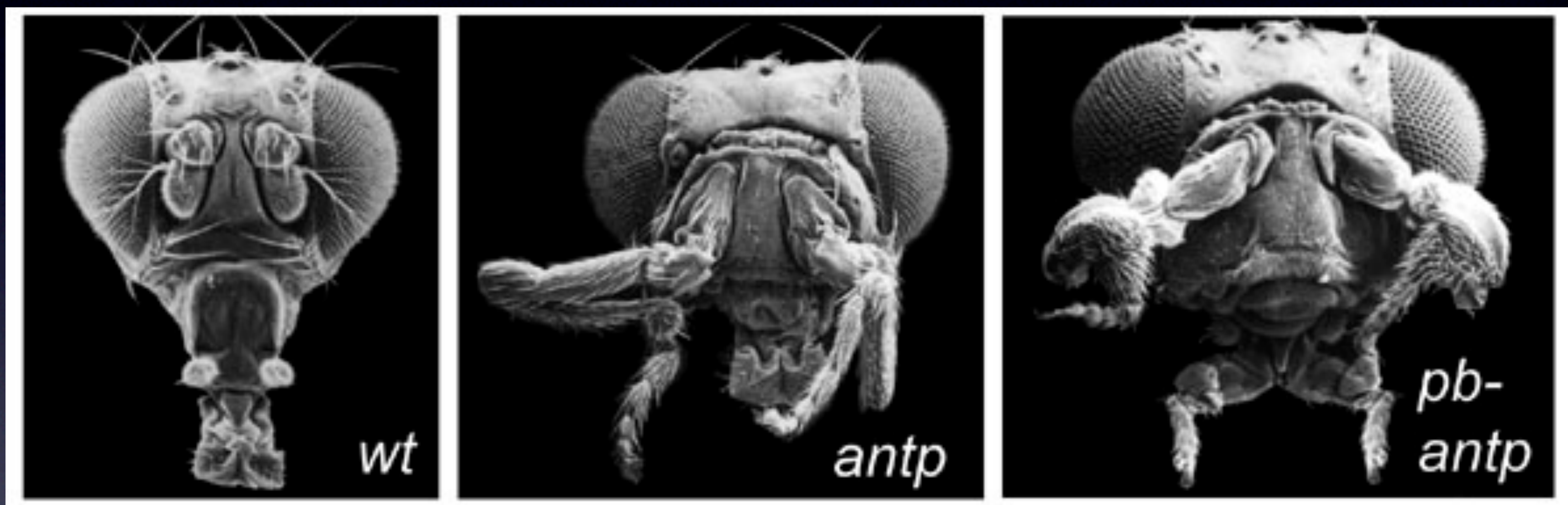
Jessica Flack
Santa Fe Institute
http://www.santafe.edu/~jflack



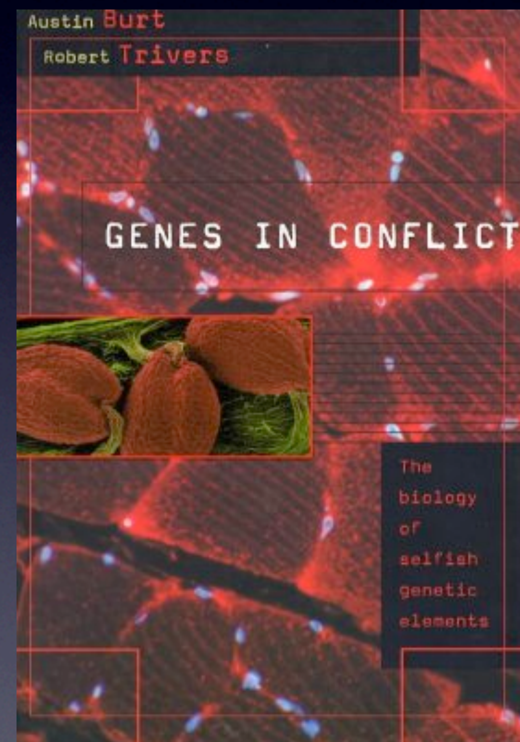
An interaction map of the yeast proteome from published interactions. Proteins are colored coded by function. Schwikowski, Uetz & Fields (2000) A network of interacting proteins in yeast. Nat. Biotechnol. 18, 1257-1261.

Experimental approaches to studying robustness in complex systems using networks and 'knockout' methods


MICHAEL TURNER

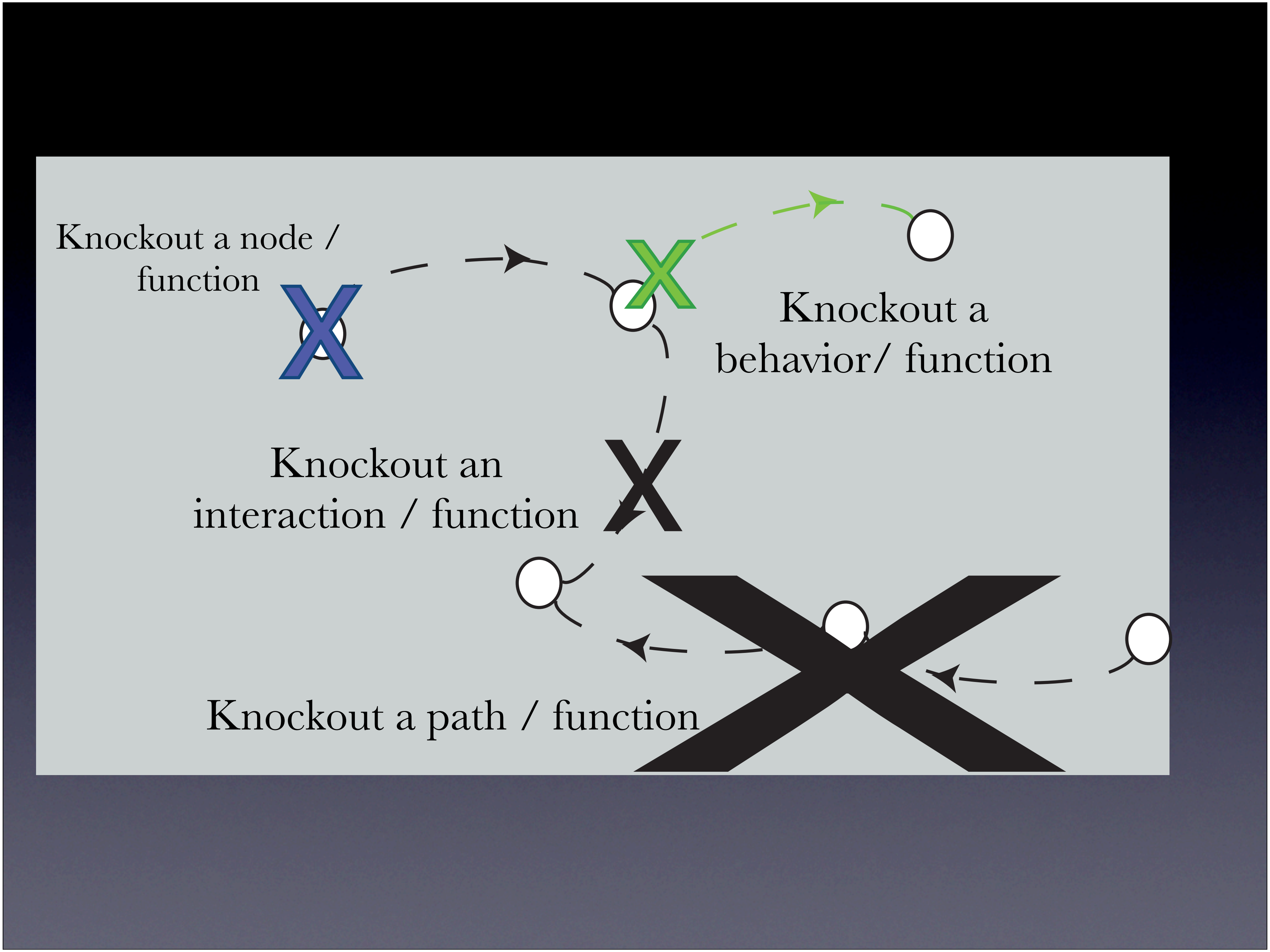


Mutations can cause loss of function, loss of function decreases organismal fitness



Severe conflicts jeopardize organizational stability; reduced stability reduces individual fitness (and societal) fitness

System property *A* is robust if it remains invariant despite perturbation *X* that disables or removes adaptive component *B*.

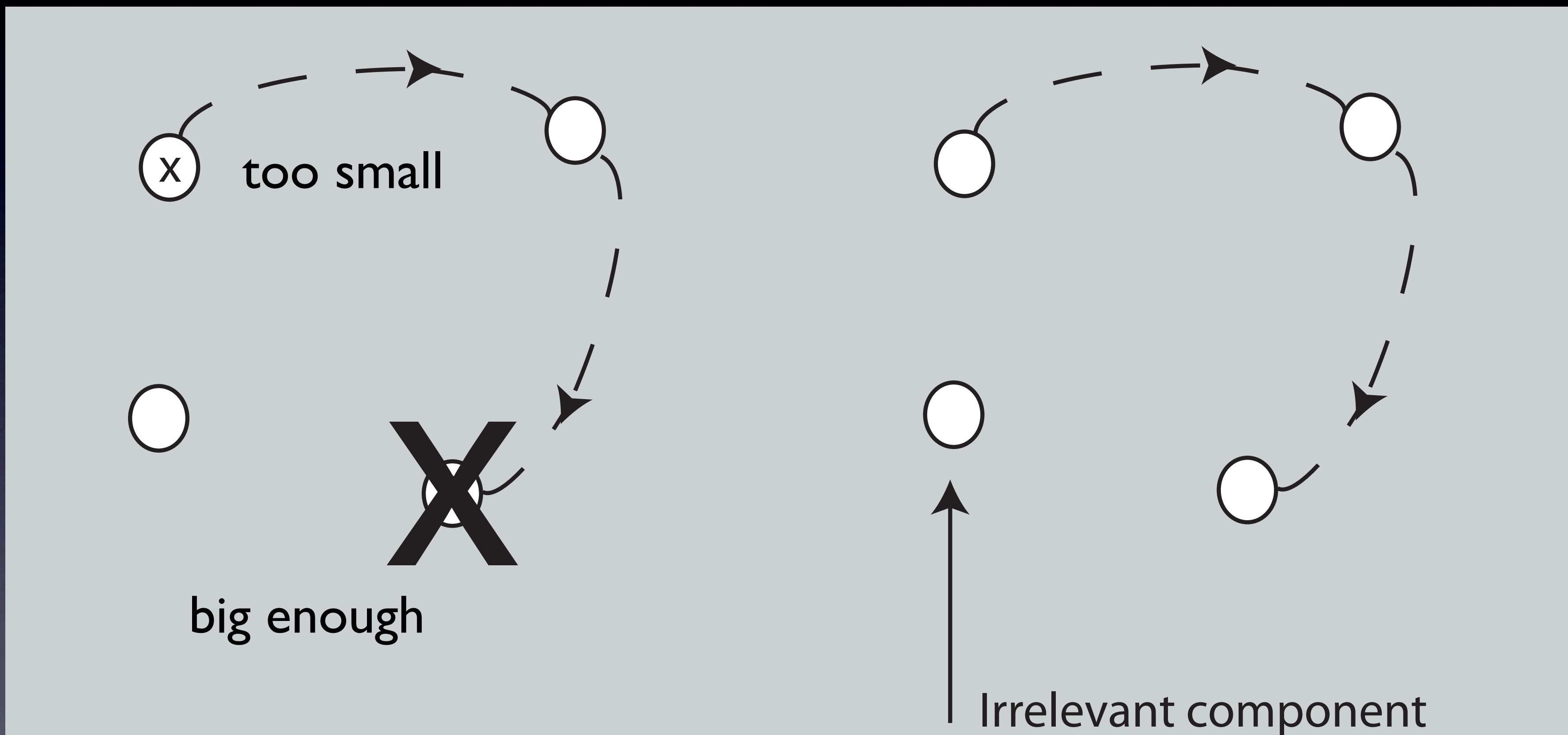


Knockout a node / function
Knockout a behavior/ function
Knockout an interaction / function
Knockout a path / function

Examples of Perturbation X

removal of high degree or random selection of nodes (e.g. predation event, internet attack)
environmental uncertainty (e.g. fluctuating availability of food)
noise / error (e.g. germ-line mutation)
chronic conflict (e.g. competition over status; social transgressions, fighting over resources)

Non-trivial Robustness



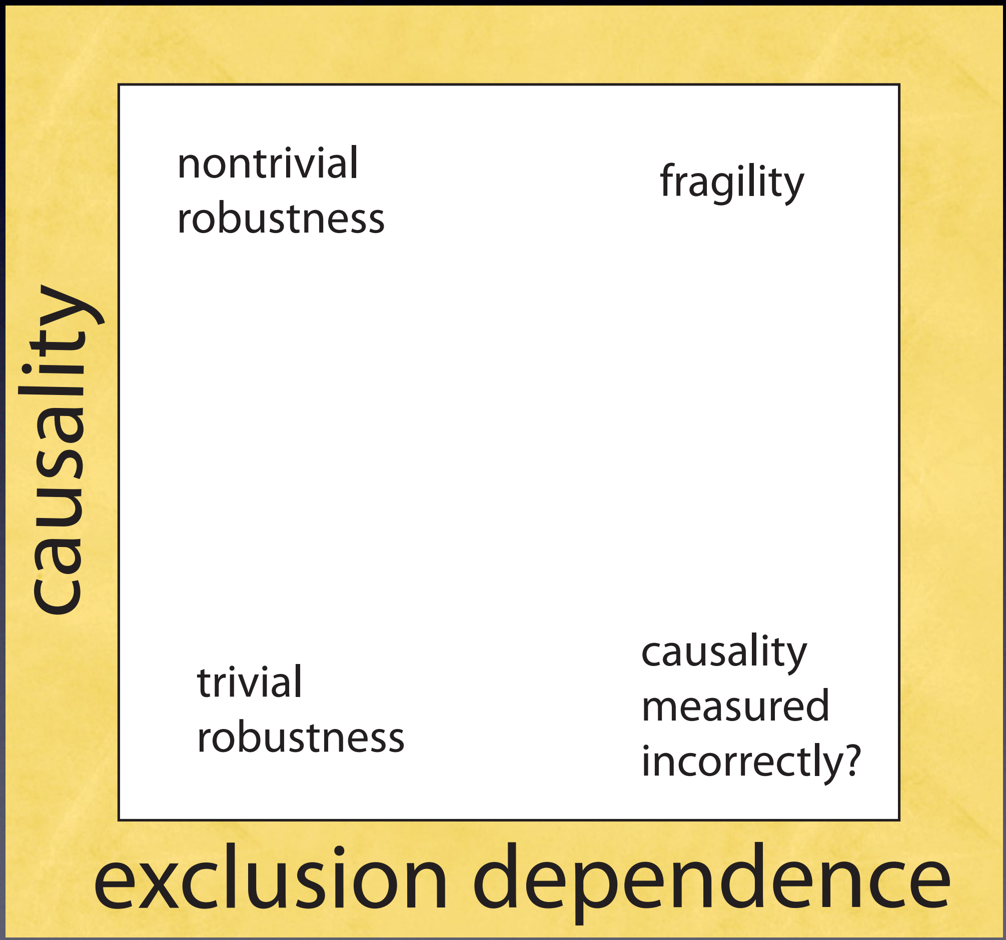
Relevant Perturbation

Causally-relevant Component

CAUSALITY (relevance/ adaptive value)	unperturbed contribution of component *B* to system property/ function *A*
EXCLUSION DEPENDENCE	change in *A* with perturbation to *B*

Robustness of a system property *A* to knockout of *B* can be defined as

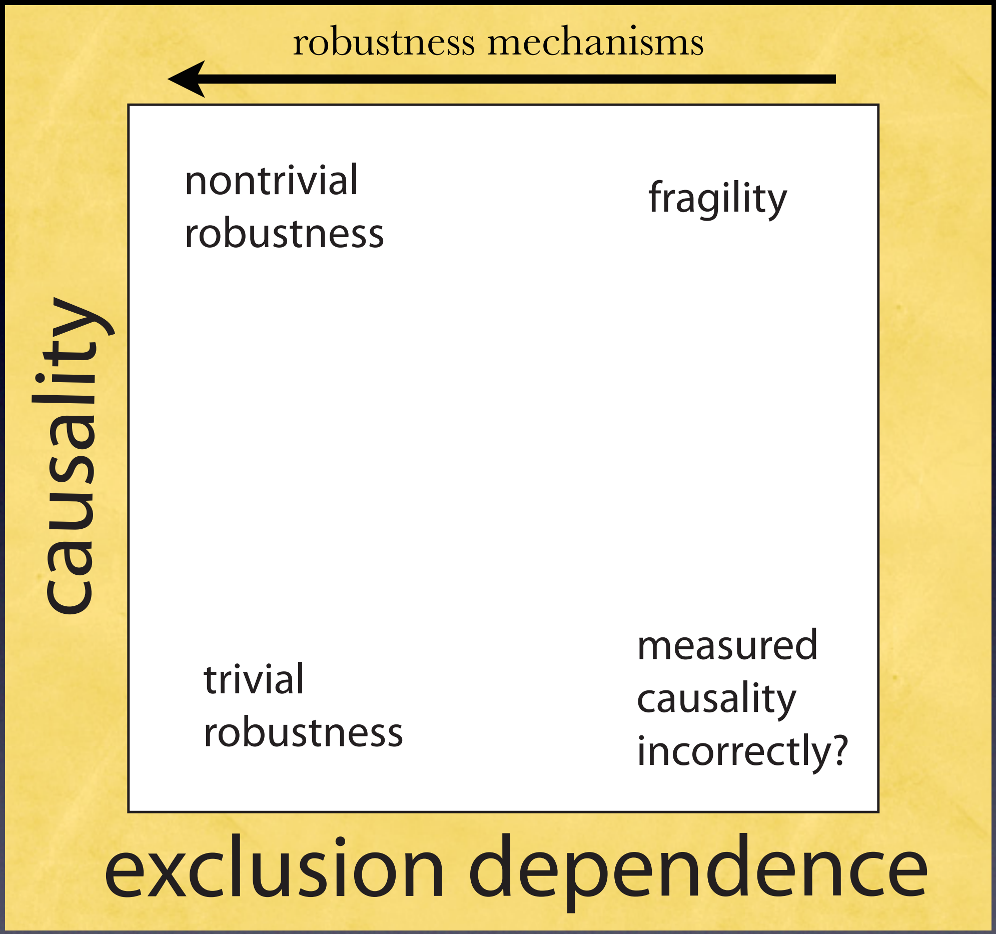
Causality (how much B contributes) minus Exclusion Dependence (how much A changes in absence of B)



see Ay, N., Flack, J.C., Krakauer, D.C. 2007. Robustness and complexity co-constructed in multimodal signaling networks, Phil Trans, 362, 441-447

Component C is a robustness mechanism if

it reduces variance in system property A under perturbation of adaptive component B



Robustness mechanisms reduce exclusion dependence

X: perturbation

A: system property (exclusion dependence)

B: adaptive component (causal contribution)

C: robustness mechanism

Designing Experiments to Test For:

Robustness Mechanism

Is *C* a robustness mechanism that prevents *A* from changing in response to perturbation of *B*?

Is System Robust?

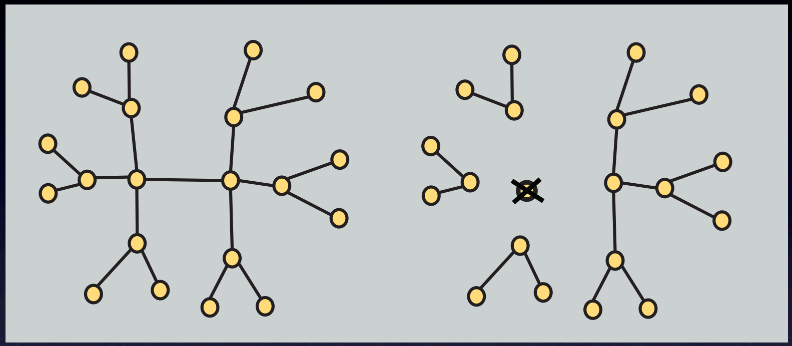
Is system property *A* robust to knockout of adaptive component *B*?

System Robustness & Robustness Mechanism

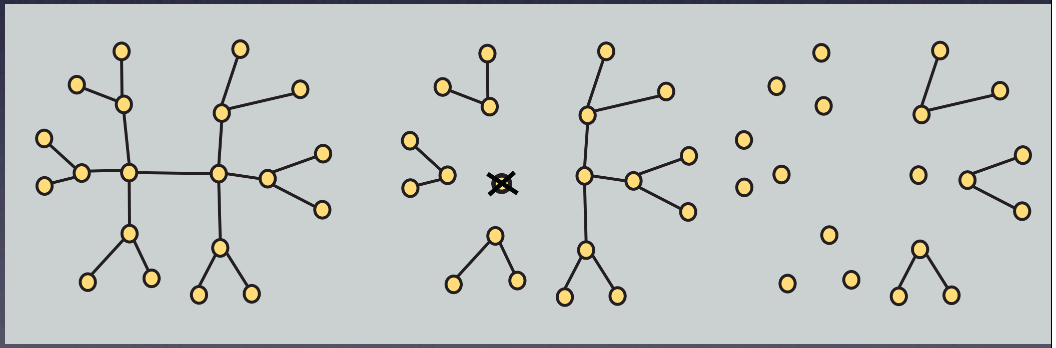
Is system property *A* robust to knockout of robustness mechanism *C*?

Two Major Types of Causal Contribution
(in terms of experimental design)

Structural Contribution



Dynamical Contribution

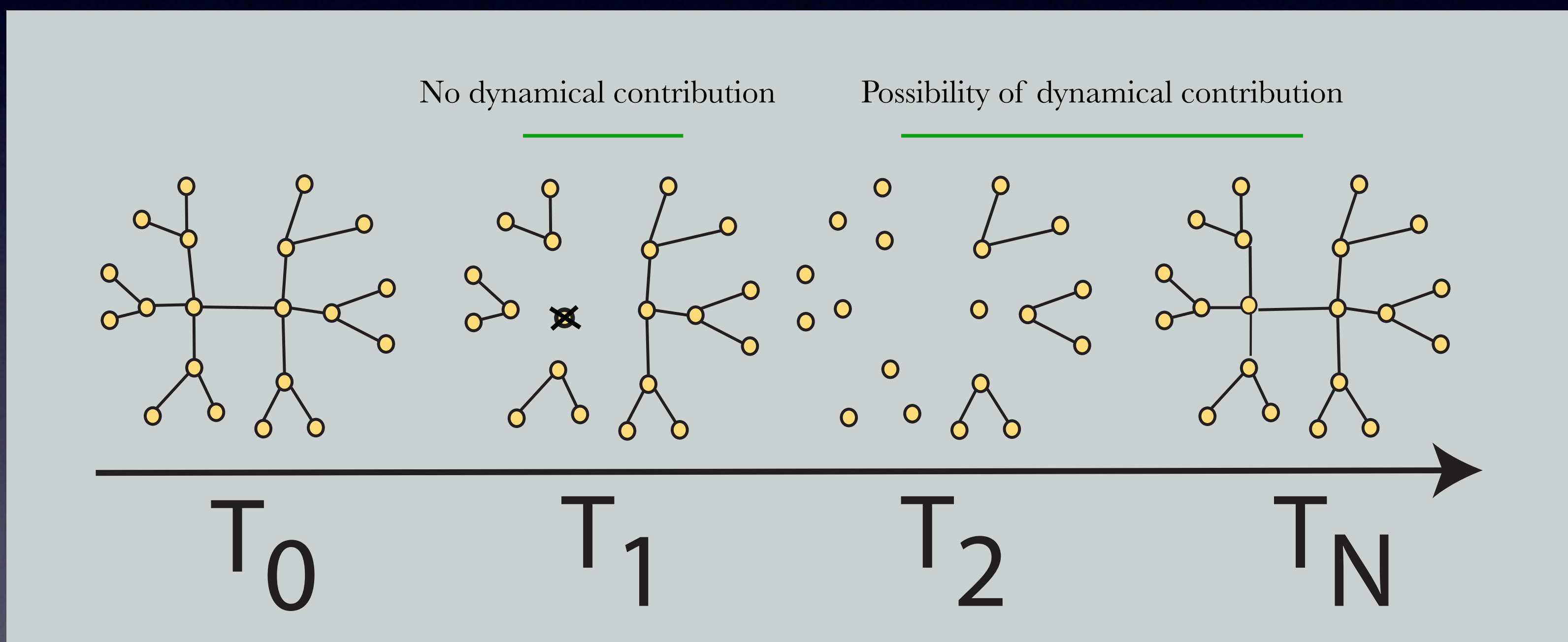


Choosing an Appropriate Timescale for Experimental Knockout

Knockout to evaluate how robust system is

Knockouts to Evaluate Robustness Mechanism

Pre Knockout	Instantaneous Knockout	Short-timescale Knockout	Long-timescale Knockout



Baseline/Control	Structural/Topological Contribution	Compensation through Robustness Mechanism or Destabilization / Loss of Function	Restoration, Adaptation or Failure

Error and attack tolerance of complex networks

nature

Réka Albert, Hawoong Jeong & Albert-László Barabási

Department of Physics, 225 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556, USA

Molecular Systems Biology 3; Article number 86; doi:10.1038/msb4100127
Citation: *Molecular Systems Biology* 3:86

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molecular systems biology

Backup without redundancy: genetic interactions reveal the cost of duplicate gene loss

Jan Ihmels[1,2,3,*], Sean R Collins[1,2,3], Maya Schuldiner[1,2,3], Nevan J Krogan[1,2] and Jonathan S Weissman[1,2,3]

Policing stabilizes construction of social niches in primates

nature

Jessica C. Flack[1,2,3], Michelle Girvan[1], Frans B. M. de Waal[2,3] & David C. Krakauer[1]

Robustness to loss of robustness mechanism with high cost during restoration

Jessica C. Flack, Brenda McCowan, & David C. Krakauer (STUDY UNDERWAY)

Error and attack tolerance of complex networks

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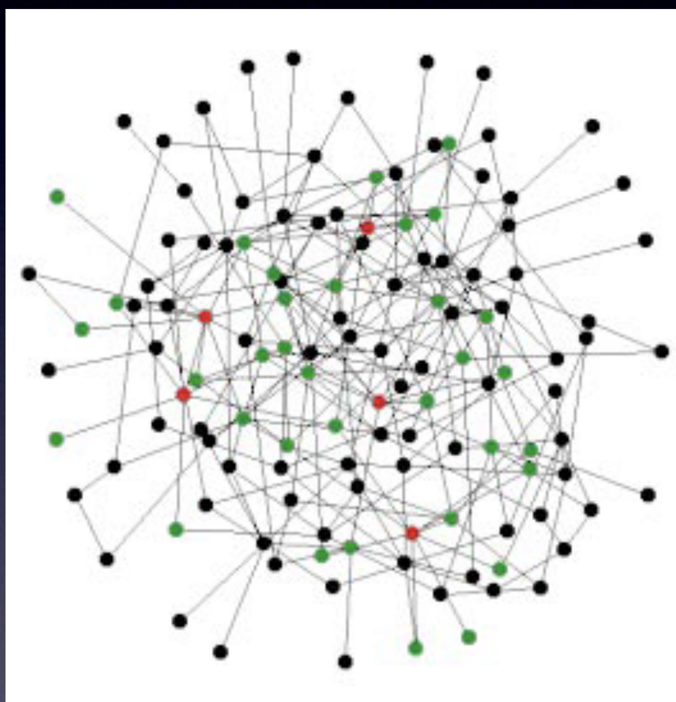
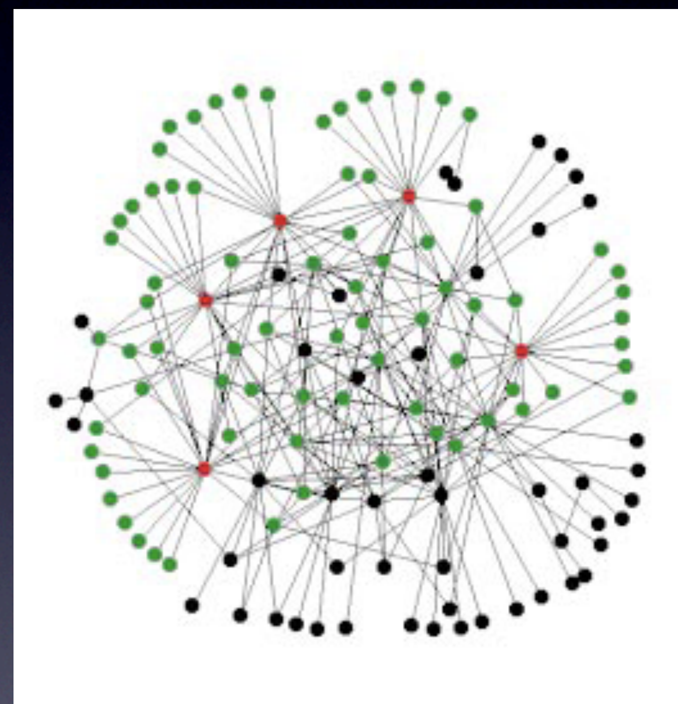
Case Study 1



exponential

nodes have approximately same number of links
only 27% of nodes reached by five most connected nodes
130 nodes, 215 links



scale-free

majority of nodes have one or two links, few have many links; thus wiring is inhomogenous; 60 % of nodes reached by five most connected nodes; 130 nodes, 215 links

Error and attack tolerance of complex networks

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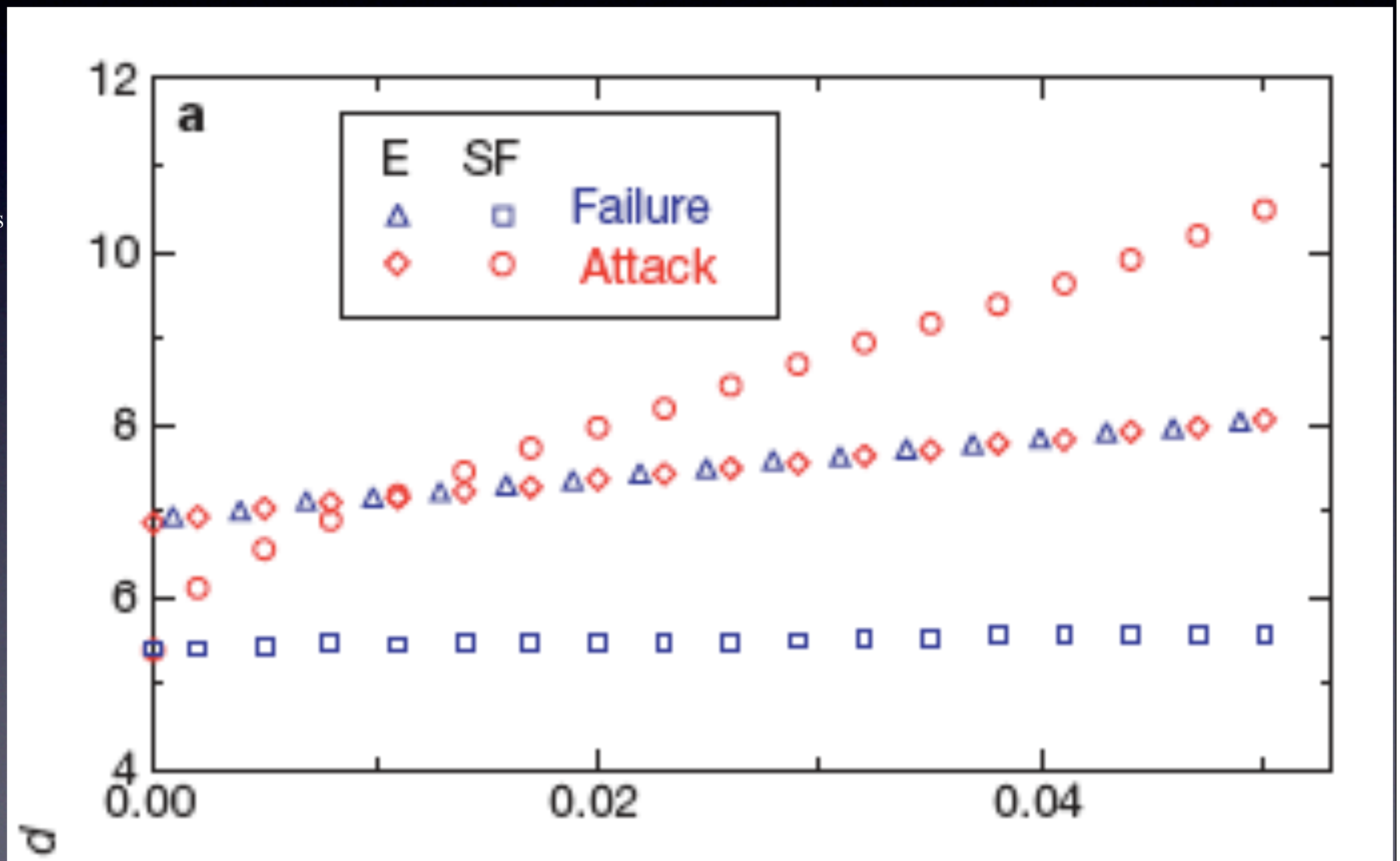
10,000 nodes
20,000 links
d: diameter
x-axis: fraction nodes removed



Error and attack tolerance of complex networks

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Department of Physics, 225 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556, USA

perturbation X	adaptive component B (causal contribution)	system property A (exclusion dependence)	robustness mechanism C
random removal (mimics error/ failure) ——— targeted removal of high-degree nodes (mimics targeted attack)	connectivity (degree)	network diameter / information flow efficiency	scale-free network wiring confers robustness against random removals

Error and attack tolerance of complex networks

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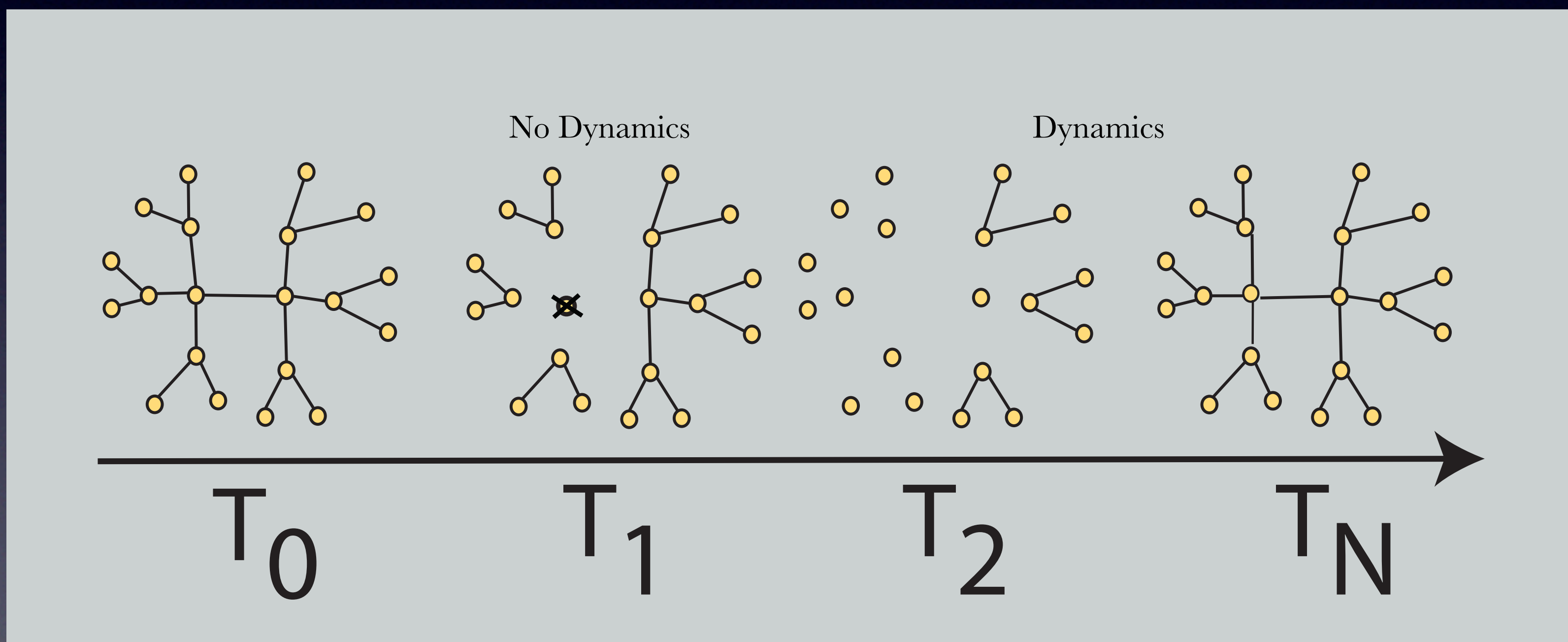
Is *C* a robustness mechanism that prevents *A* from changing in response to knockout of *B*?

Pre Knockout | Instantaneous Knockout | Short-timescale Knockout | Long-timescale Knockout



Baseline/Control

Structural/Topological Contribution

Compensation through Robustness Mechanism or Destabilization / Loss of Function

Restoration, Adaptation or Failure

Robustness against mutation in genetic networks of yeast

Andreas Wagner — Nature Genetics 2000

Role of duplicate genes in genetic robustness against null mutations

Zhenglong Gu*†, Lars M. Steinmetz‡†, Xun Gu§, Curt Scharfe‡, Ronald W. Davis‡ & Wen-Hsiung Li* — Nature 2003

Molecular Systems Biology 3; Article number 86; doi:10.1038/msb4100127
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Backup without redundancy: genetic interactions reveal the cost of duplicate gene loss

Jan Ihmels[1,2,3,*], Sean R Collins[1,2,3], Maya Schuldiner[1,2,3], Nevan J Krogan[1,2] and Jonathan S Weissman[1,2,3]

Case Study 2

observation: many genes can be deleted without phenotypic consequences

two hypothesized robustness mechanisms C:

1. gene duplication (back-up compensation due to presence of paralogs--multiple genes in genome with similar sequences)

2. alternative metabolic pathways or regulatory networks

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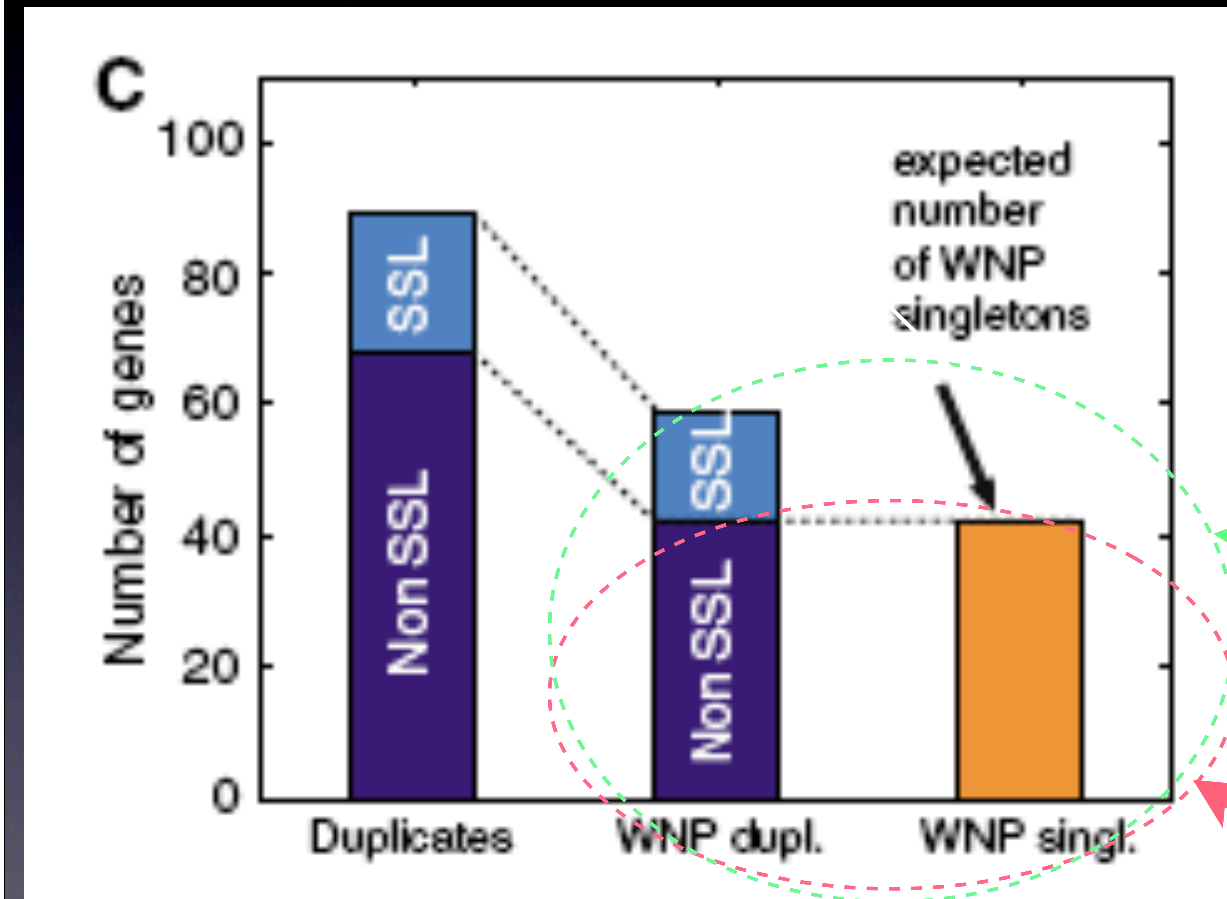

WNP: does not show a strong effect on phenotype

Gu et al. find a difference but do not know why; larger sample size but no double simultaneous double deletions

Wagner finds no difference: sample size too small, no simultaneous double deletions

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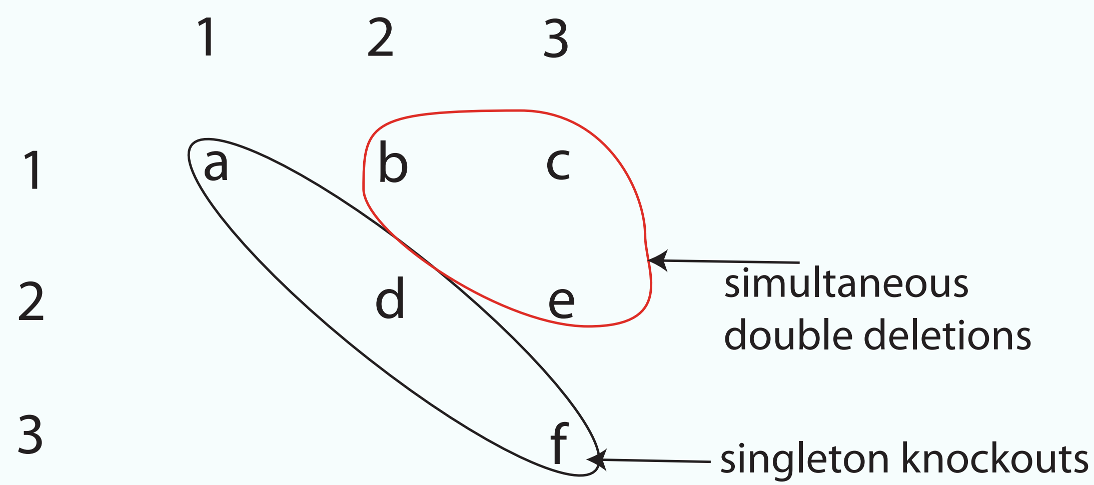

“SSL” duplicate genes: b > a + d

“NSSL” duplicate genes: c ~ a + f; e ~ d + f

Basically idea is to use simultaneous double gene deletions coupled to short-time scale knockout to determine how gene-gene dependencies effect phenotype / fitness

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perturbation *X*	adaptive component *B* (causal contribution)	system property *A* (exclusion dependence)	robustness mechanism *C*
mutation	e.g. DNA damage repair, transcriptional regulation, chromosome segregation	e.g. cell growth or viability	multiple: duplicate genes play a small role through backup compensation (but mechanism is not redundancy)

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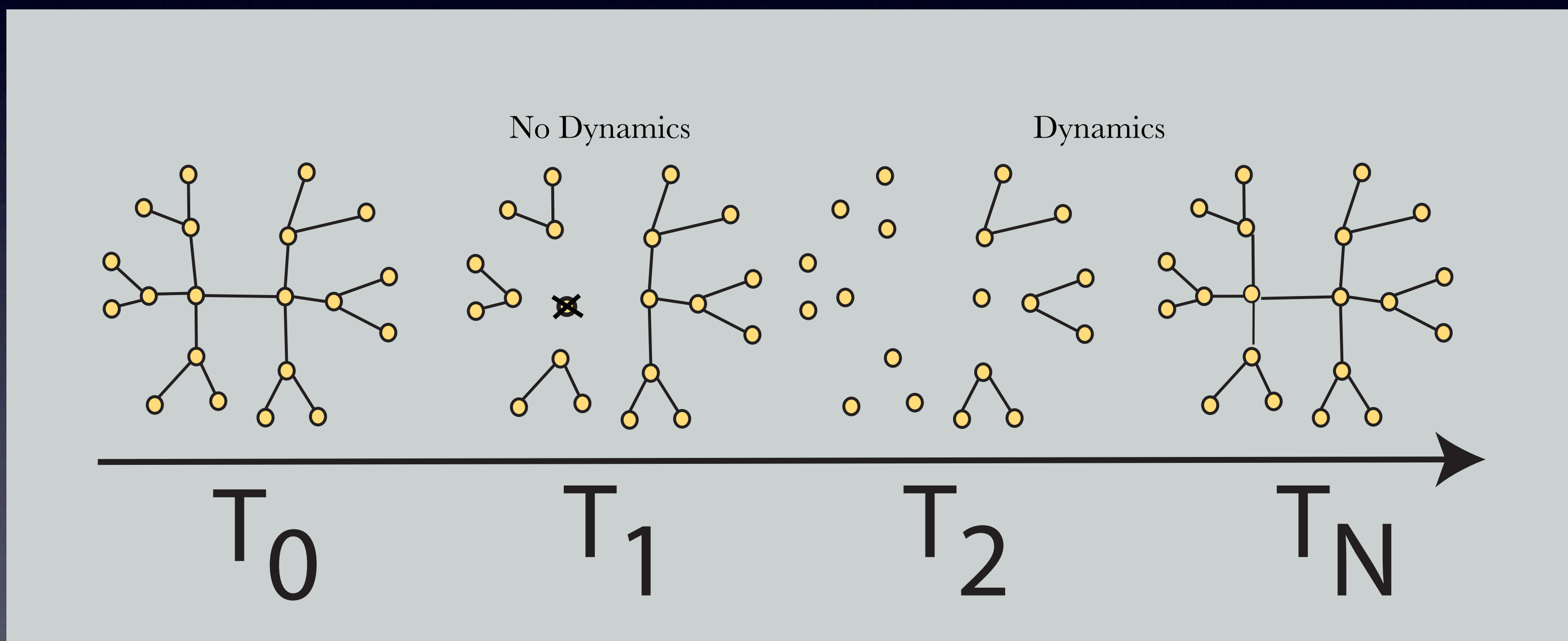
Is *C* a robustness mechanism that prevents *A* from changing in response to knockout of *B*?

Pre Knockout | Instantaneous Knockout | Short-timescale Knockout | Long-timescale Knockout



Baseline/Control

Structural/Topological Contribution

Compensation through Robustness Mechanism or Destabilization / Loss of Function

Restoration, Adaptation or Failure

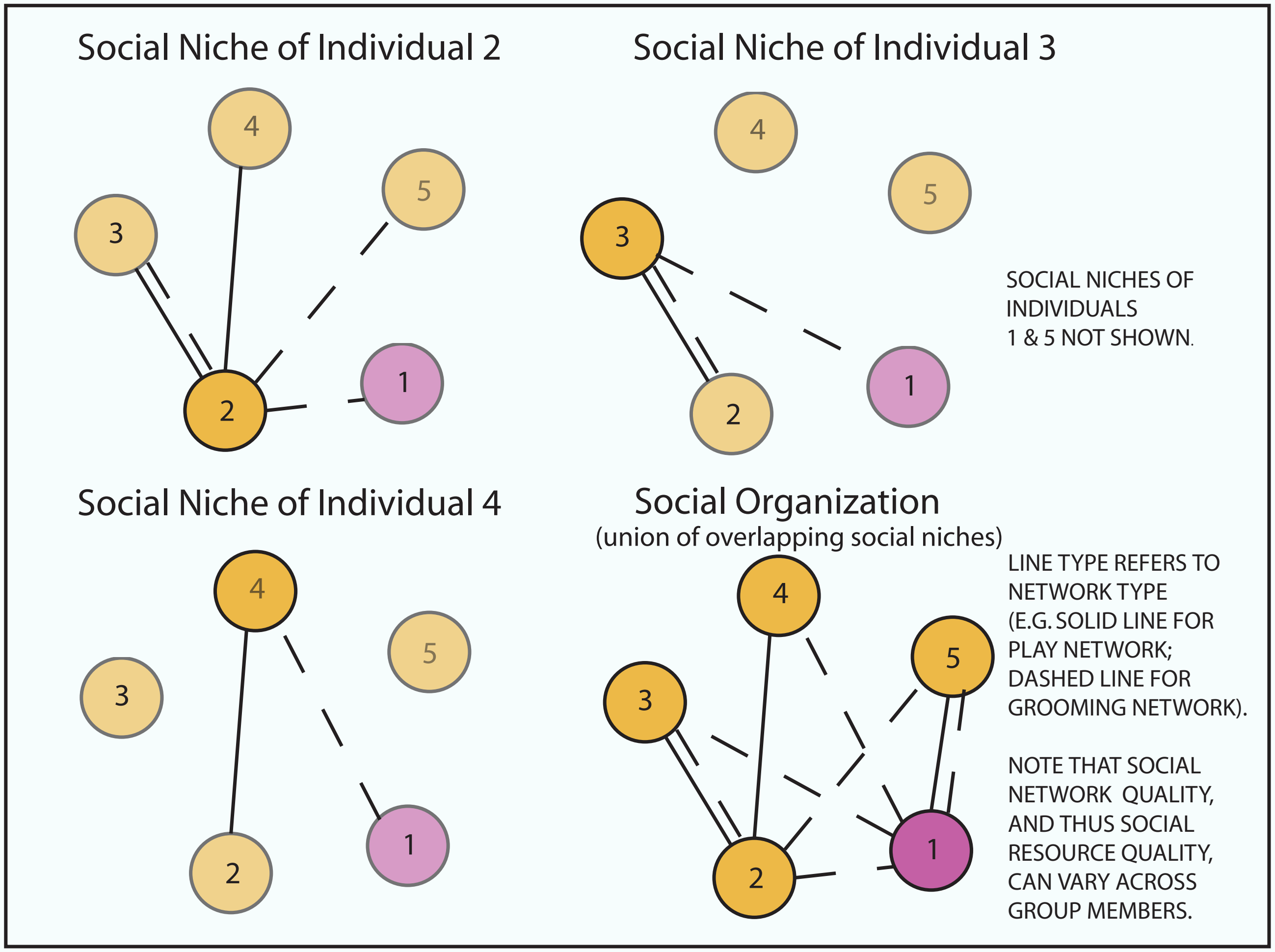
Policing stabilizes construction of social niches in primates

Jessica C. Flack[1,2,3], Michelle Girvan[1], Frans B. M. de Waal[2,3] & David C. Krakauer[1]

observation one: chronic conflict in social systems
observation two: in some systems third-parties (police) manage conflict by breaking up fights

question: why isn't conflict destabilizing?

hypothesis: policing is a robustness mechanism, which by controlling conflict ensures individuals can interact at low cost and build high quality social niches



Whereas the ecological niche is composed of resource vectors (availability of wood, prey items, etc), the social niche is composed of an individual's vector of behavioral interactions in the networks in which it participates

Policing stabilizes construction of social niches in primates

Jessica C. Flack[1,2,3], Michelle Girvan[1], Frans B. M. de Waal[2,3] & David C. Krakauer[1]

knockout policer; assess how edge construction rules change in absence of policer

Policing stabilizes construction of social niches in primates

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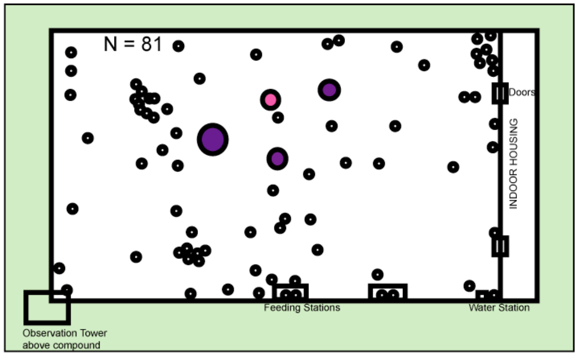
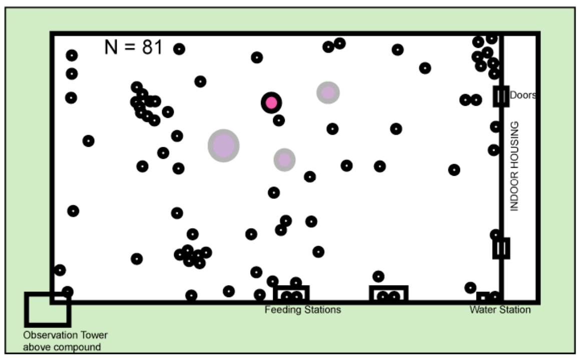
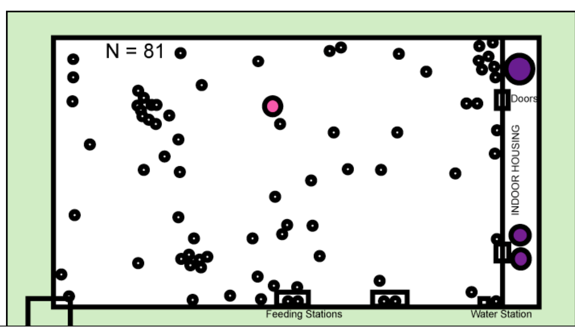
Experimental Setup



Normal Condition



Topological Knockout Condition



Experimental Knockout Condition

partial knockout-isolation of one function

Policing stabilizes construction of social niches in primates

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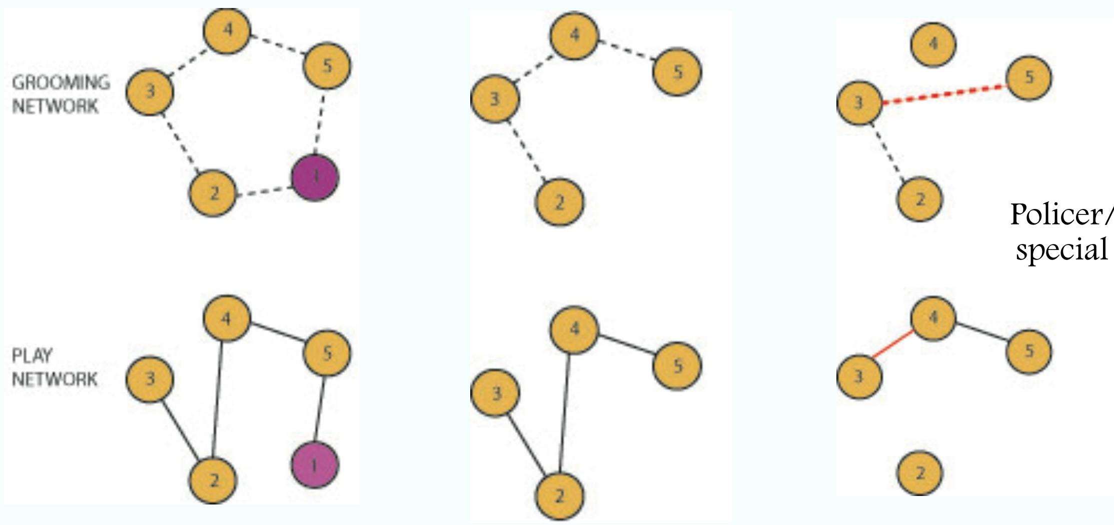
short-timescale, temporary, & partial knockout of policing mechanism by removing policer

Observed | Topological | Experimental



Policer/ purple node plays no special role in these networks

measures structural contribution of knockout nodes

exclusion dependence value of node without specifying whether value is due to direct or indirect effects

measures whether exclusion dependence value is due to indirect effects by controlling for structural contribution of node

Policing stabilizes construction of social niches in primates

Jessica C. Flack[1,2,3], Michelle Girvan[1], Frans B. M. de Waal[2,3] & David C. Krakauer[1]

		policing. . .
network properties	degree	mean degree ↑
	local clustering	mean clustering ↓
	reach	reach ↑
	assortativity	assortativity ↓

Policing stabilizes construction of social niches in primates

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perturbation *X*	Adaptive component *B* (causal contribution)	system property *A* (exclusion dependence)	robustness mechanism *C*
chronic conflict	social niche construction	efficient and reliable social resource extraction (social niche quality)	policing

Policing stabilizes construction of social niches in primates

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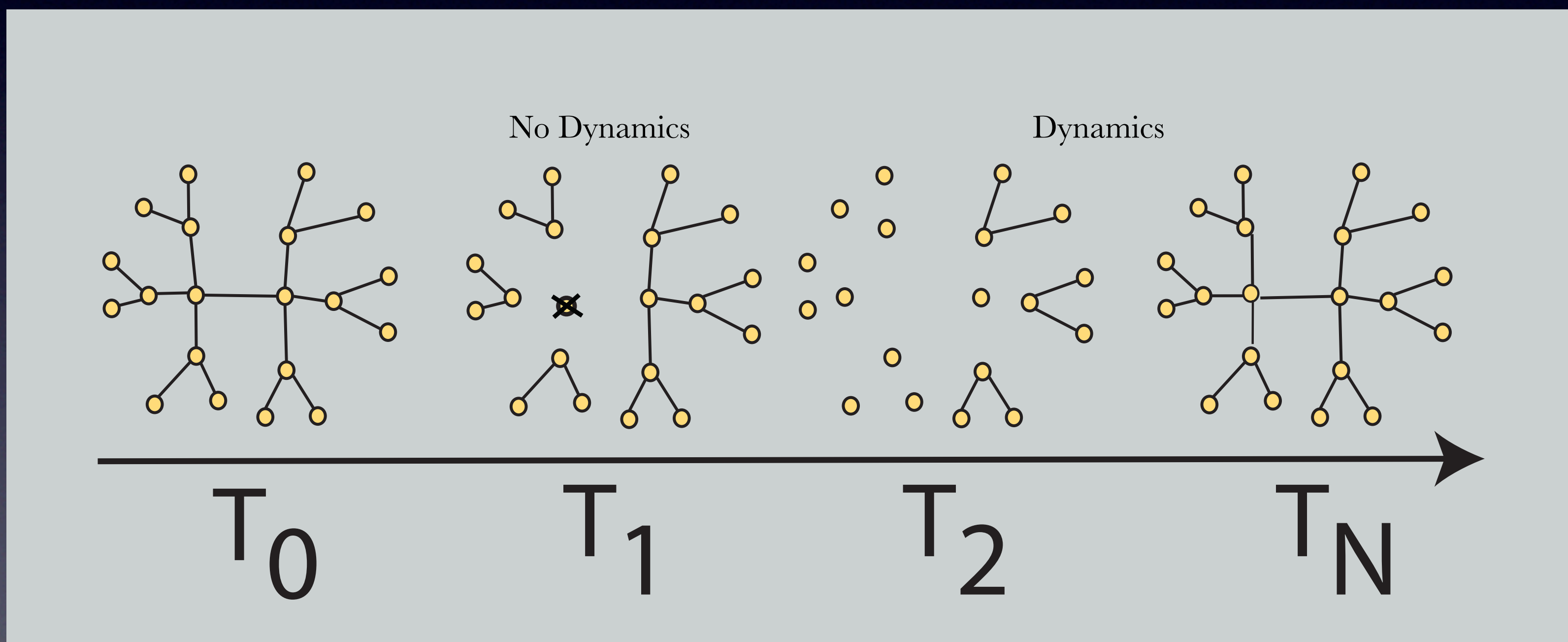
Pre Knockout

Instantaneous Knockout

Short-timescale Knockout

Long-timescale Knockout



Baseline/Control

Structural/Topological Contribution

Compensation through Robustness Mechanism or Destabilization / Loss of Function

Restoration, Adaptation or Failure

Robustness to loss of robustness mechanism with high cost during restoration

Jessica C. Flack, Brenda McCowan, & David C. Krakauer (STUDY UNDERWAY)

Case Study 4

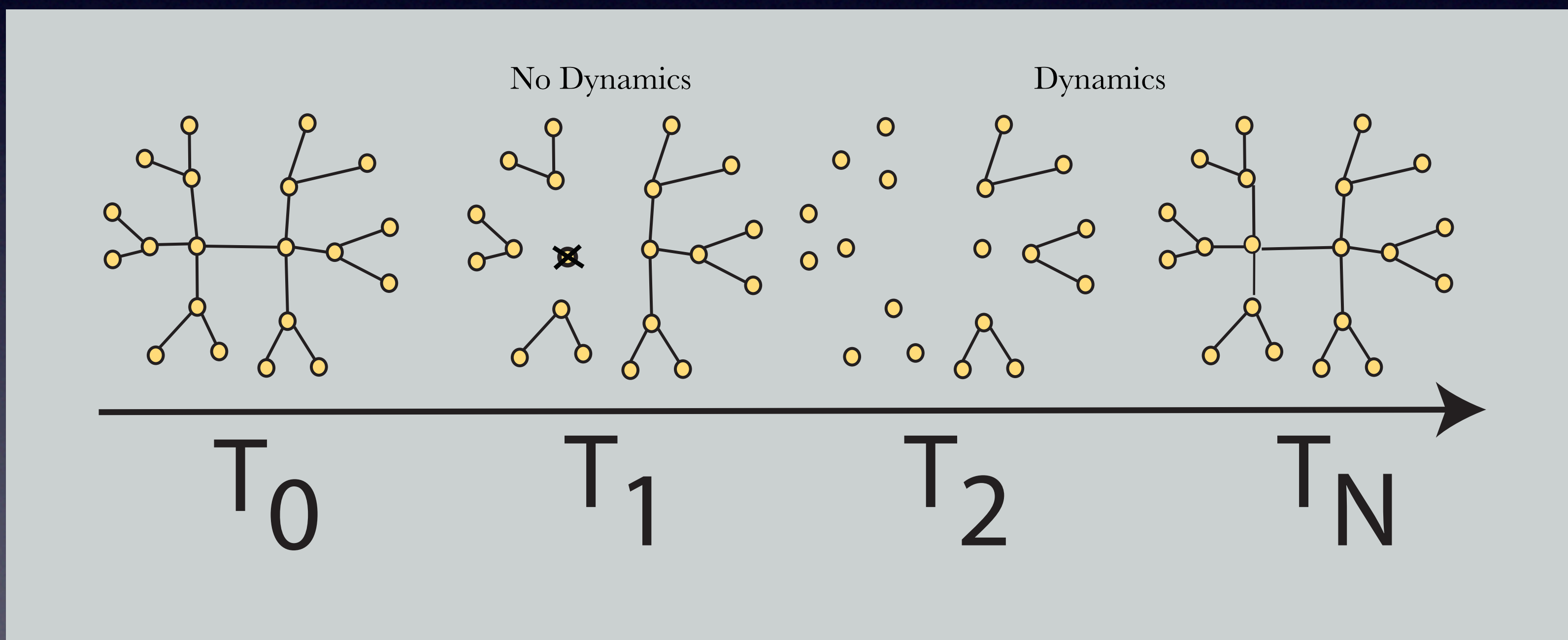
Is system property *A* robust to knockout of policing mechanism *C*?

Pre Knockout

Instantaneous Knockout

Short-timescale Knockout

Long-timescale Knockout



Baseline/Control

Structural/Topological Contribution

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Restoration, Adaptation or Failure

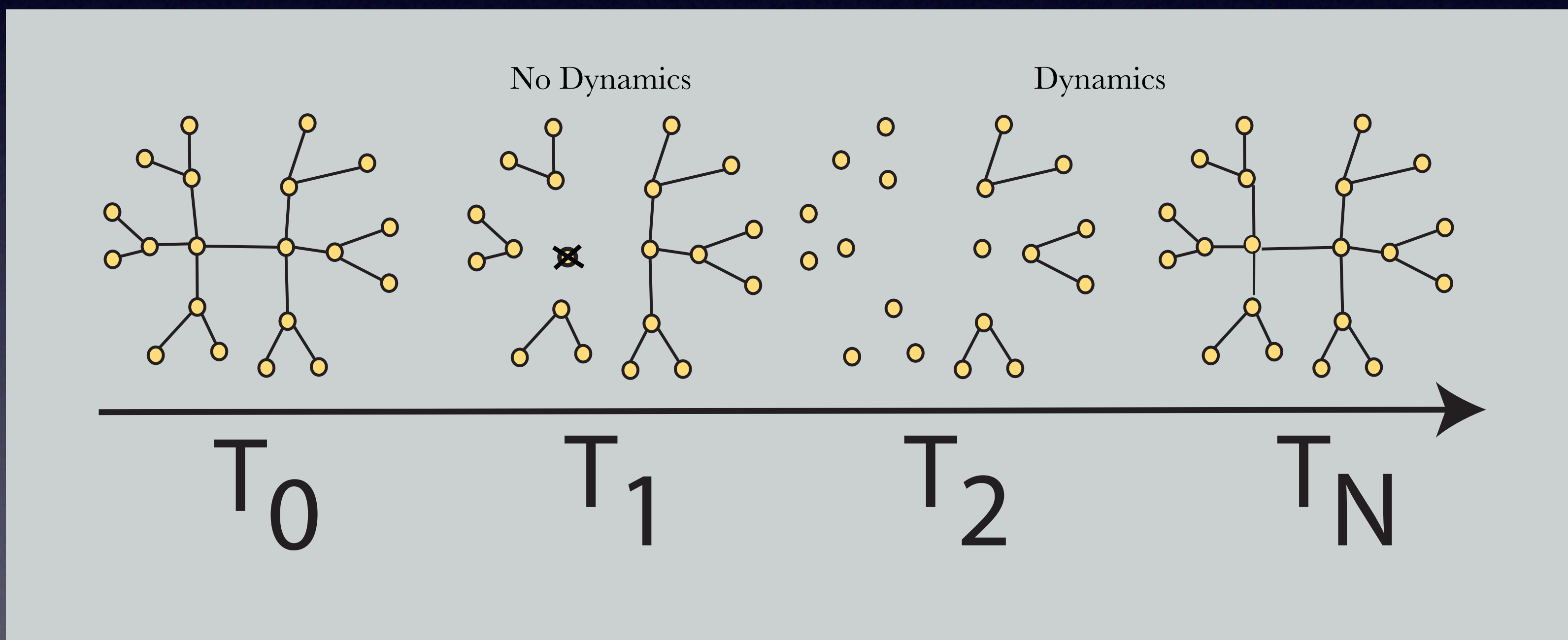
Robustness to loss of robustness mechanism with high cost during restoration

Jessica C. Flack, Brenda McCowan, & David C. Krakauer (STUDY UNDERWAY)

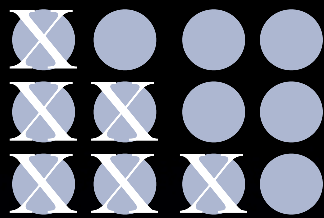
Is system property A robust to knockout of policing mechanism C?

perturbation *X*	adaptive component *B* (causal contribution)	system property *A* (exclusion dependence)	<u>back up</u> robustness mechanism *C*)
e.g. predation	low-cost interactions	efficient & reliable social resource extraction	?

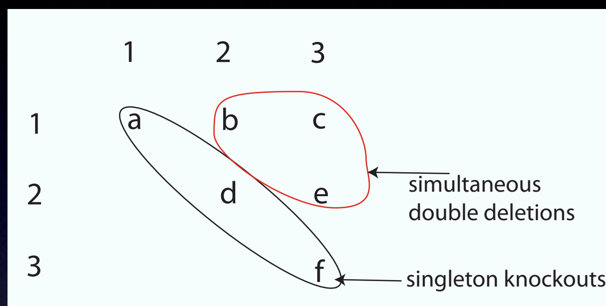
	Case Study 1 Barabasi	Case Studies 2 & 3 Wagner/Gu/Imhels Flack-Krakauer	Case Study 4 Underway
Pre Knockout	Instantaneous Knockout	Short-timescale Knockout	Long-timescale Knockout



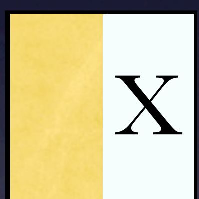
Baseline/Control	Structural/Topological Contribution	Compensation through Robustness Mechanism or Destabilization / Loss of Function	Restoration, Adaptation or Failure



Alberts, Jeong, Barbasi Study: Multiple, cumulative knockouts



Ihmels et al. Study: simultaneous double deletions of duplicates



Flack et al. Study: Isolate one function/role/behavior/mechanism through partial knockout

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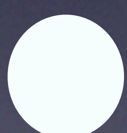
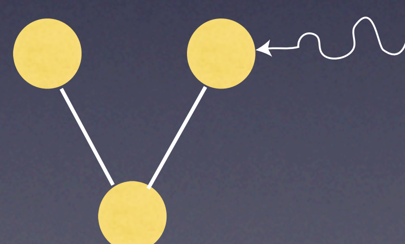


= constant



clamping

inject ‘information’, add nodes, etc.

Jianzhi Zhang, TRENDS, vol 18, 292-298 (2003)

Ay, N., Flack, J.C., Krakauer, D.C. 2007. Robustness and complexity co-constructed in multimodal signaling networks, Phil Trans, 362, 441-447

Wagner, A. Robustness against mutations in genetic networks of yeast. Nat. Gen vol 324 355-361 (2000)

Gu et al. Role of duplicate genes in genetic robustness against null mutations. Nature, Vol 421, 63-66 (2003)

Flack, J.C., Girvan, M., de Waal, F.B.M., & Krakauer, D.C. 2006. Policing stabilizes social niche construction in primates, Nature, 439, 426-429

Albert, R., Jeong, H., & Barbasi, A.L. 2000. Error and attack tolerance of complex networks, Nature, 406, 378-381

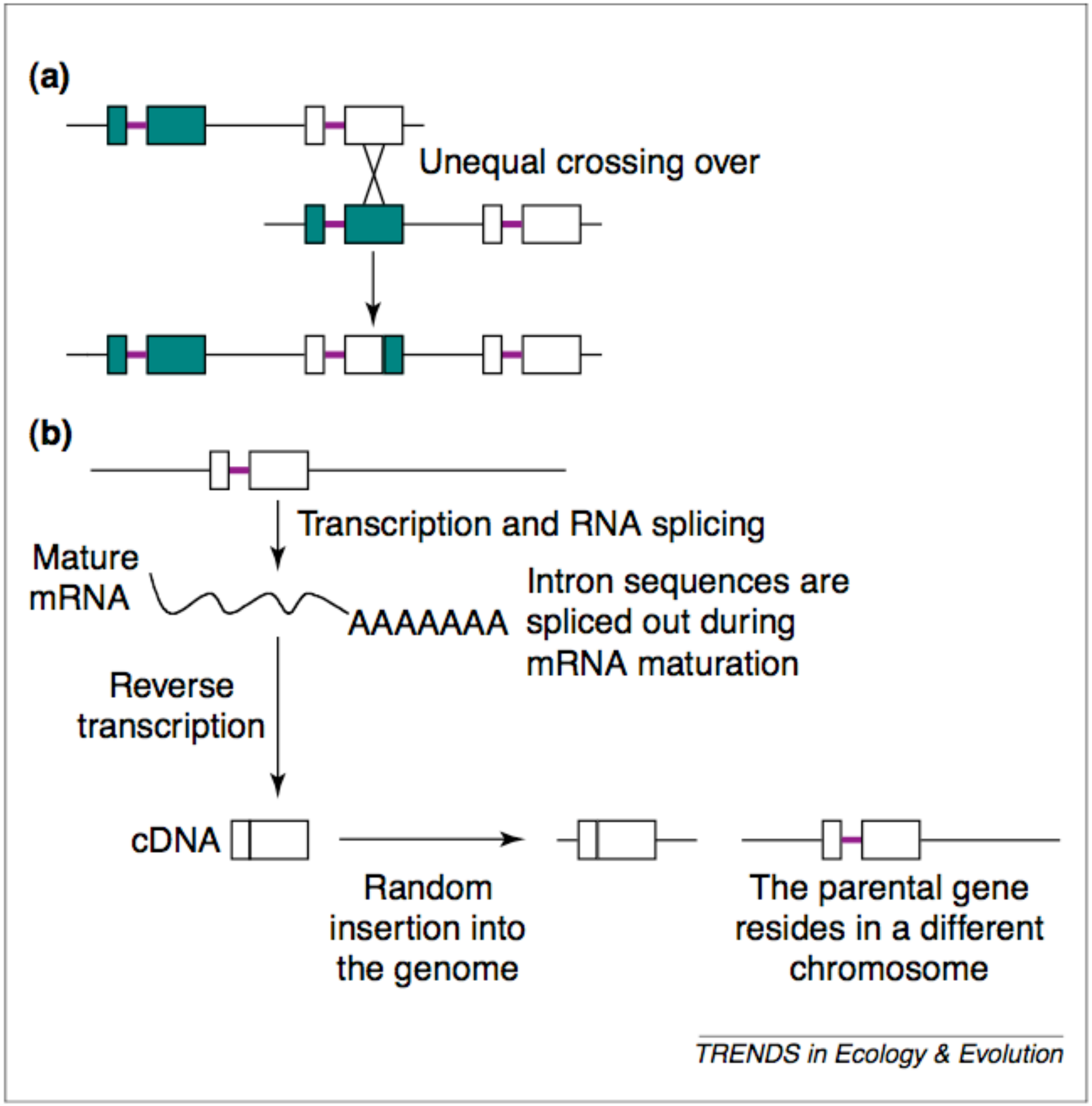
Flack, J.C., Krakauer, D.C., & de Waal, F.B.M. 2005. Robustness mechanisms in primate societies: a perturbation study, Proceedings of the Society, Series B.

Policing stabilizes construction of social niches in primates

Jessica C. Flack[1,2,3], Michelle Girvan[1], Frans B. M. de Waal[2,3] & David C. Krakauer[1]

		definition	benefit	cost	policing. . .
network properties	degree	number of nodes to which a node is connected	increased partner choice and redundancy	relationship maintenance	increases mean degree
	local clustering	density of open neighborhood of node i, where Ci = number of triangles centered on i/ number of triples centered on i	predictability	cliquishness	decreases mean clustering
	reach	measure of indirect connectedness to other nodes in the graph (2 or fewer steps)	potential for positive contagion	potential for negative contagion	increases reach/ potential for positive contagion
	assortativity	nodes of a given degree attach preferentially to nodes of similar degree	facilitates emergence of cooperation given resource disparity	social segregation	decreases assortativity / segregation without jeopardizing cooperation

Flack et al. 2006. Nature



Jianzhi Zhang, TRENDS, vol 18, 292-298 (2003)

Table 1. Prevalence of gene duplication in all three domains of life[a]

	Total number of genes	Number of duplicate genes (% of duplicate genes)	Refs
Bacteria			
Mycoplasma pneumoniae	677	298 (44)	[65]
Helicobacter pylori	1590	266 (17)	[66]
Haemophilus influenzae	1709	284 (17)	[67]
Archaea			
Archaeoglobus fulgidus	2436	719 (30)	[68]
Eukarya			
Saccharomyces cerevisiae	6241	1858 (30)	[67]
Caenorhabditis elegans	18 424	8971 (49)	[67]
Drosophila melanogaster	13 601	5536 (41)	[67]
Arabidopsis thaliana	25 498	16 574 (65)	[69]
Homo sapiens	40 580[b]	15 343 (38)	[11]

[a]Use of different computational methods or criteria results in slightly different estimates of the number of duplicated genes [12].
[b]The most recent estimate is ~30 000 [61].

Jianzhi Zhang, TRENDS, vol 18, 292-298 (2003)

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Backup without redundancy: genetic interactions reveal the cost of duplicate gene loss

Jan Ihmels[1,2,3,*], Sean R Collins[1,2,3], Maya Schuldiner[1,2,3], Nevan J Krogan[1,2] and Jonathan S Weissman[1,2,3]

How does back-up compensation work? Redundancy or partial overlap on specific functions?