lecture 10: multilevel organization of complex systems and modeling limitations

Multilevel Organization of Complex Systems

systems modeling

- Data and statistics provide **the essential basis to understand** (i) the ontogeny of systems and (ii) their evolution.
- **Machine Learning** is the **key technology** for the creation of **predictive models** and the eventual automation of decision making across different economic valuations.
- Providing analytical insights [from the currently available] huge amount of data, in real time, requires not only strong computational processing power and specific tools, but **awareness of the technical, ethical and legal complexities all along the processual pipeline.**
  - The philosophical implications of modeling from the perspective of complex systems science.

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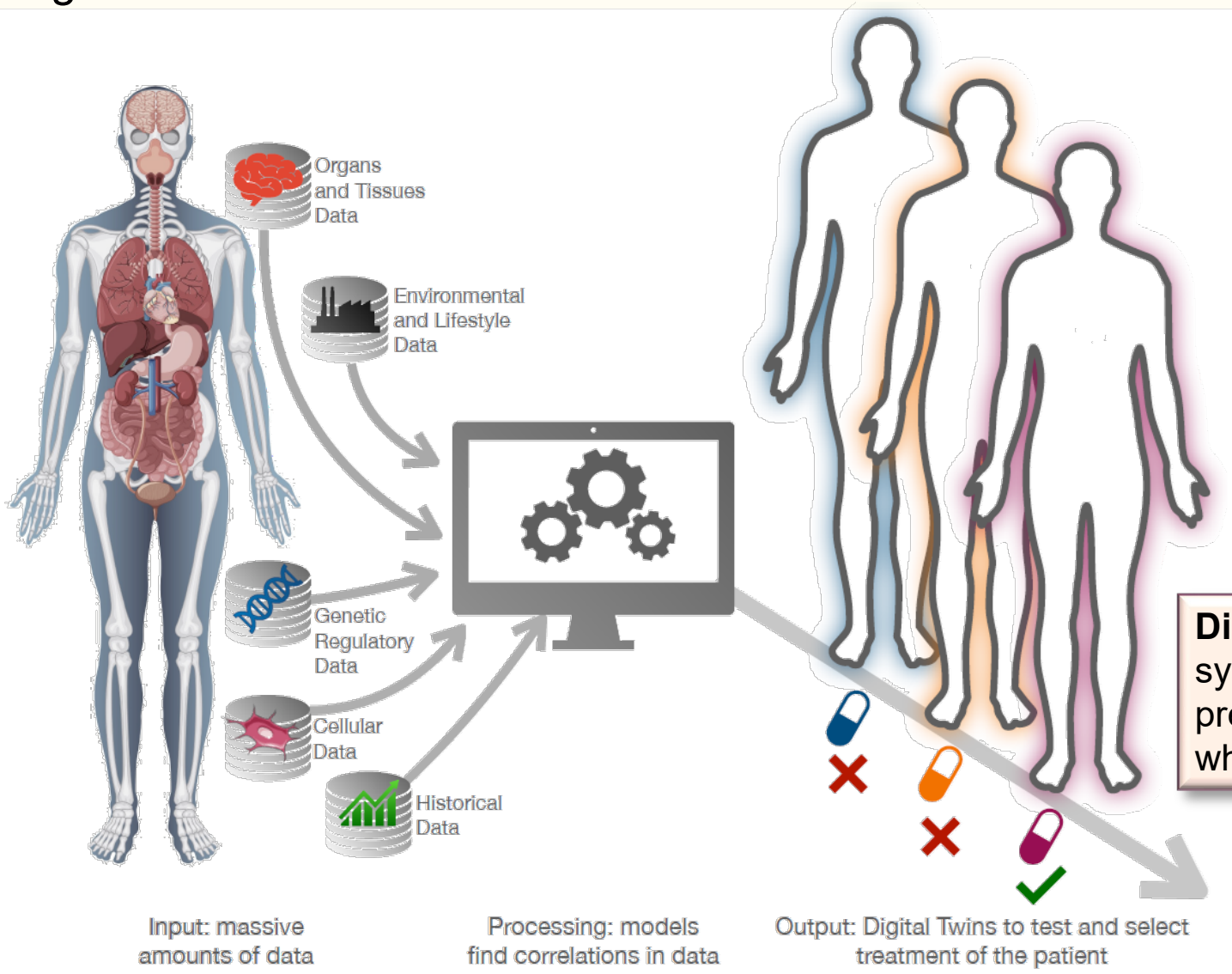
systems modeling

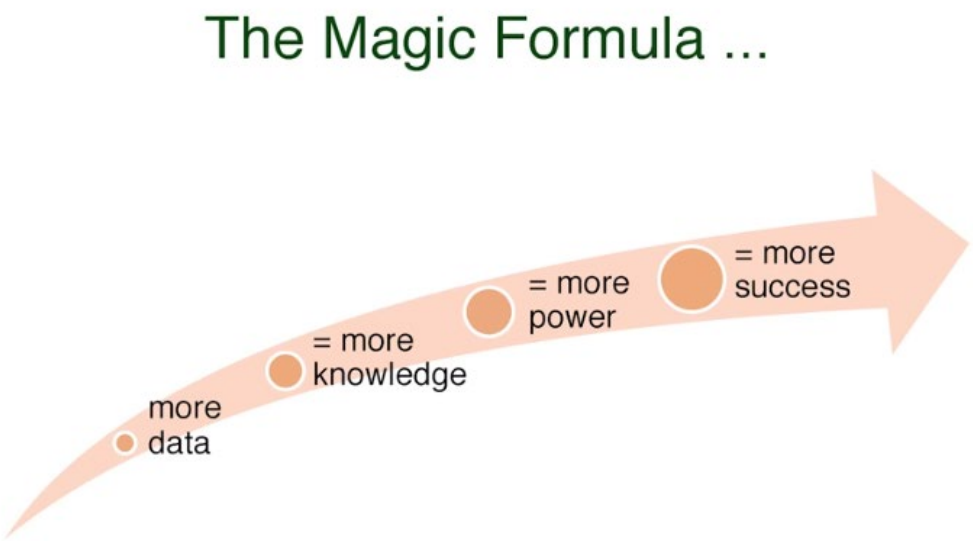
Dirk Helbing

The Magic Formula …

more data
= more knowledge
= more power
= more success

digital twins for health from human and animal data from all levels





Digital twin: in-silico *replication* of a biological cell, sub-system, organ or a whole organism with a transparent predictive model of their relevant ***causal mechanisms*** which responds in the same manner to ***interventions***.

De Domenico, et al [2025]. "Challenges and opportunities for digital twins in precision medicine: a complex systems perspective". *npj Digital Medicine* **8**, 37.

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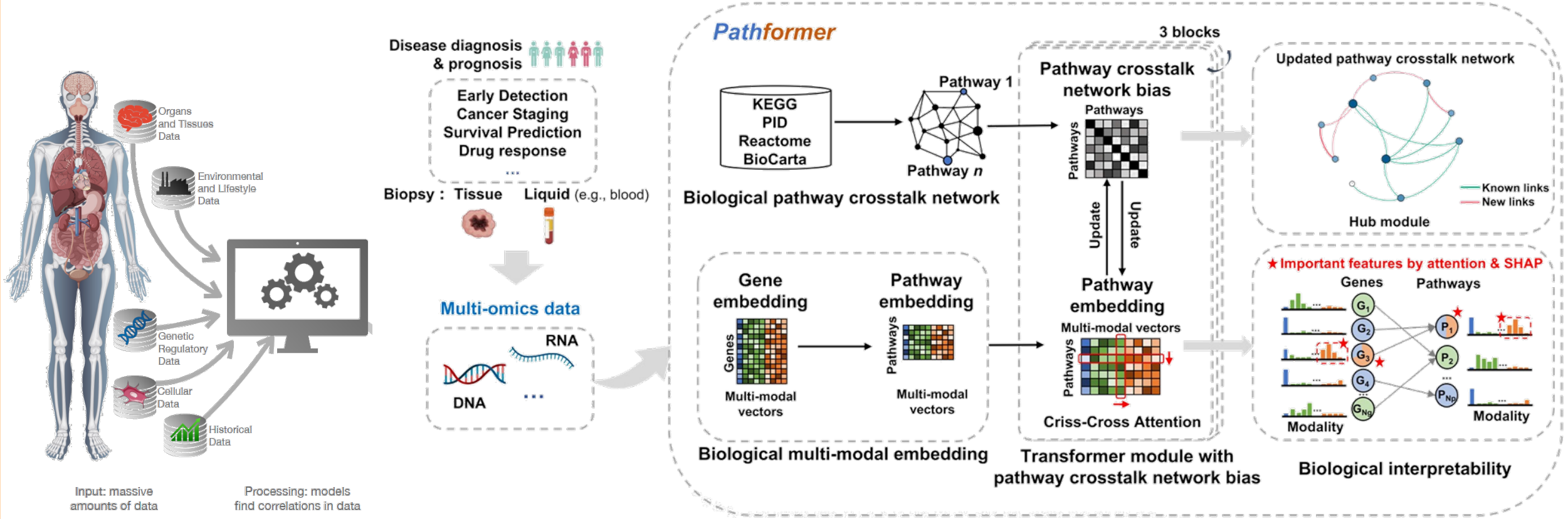
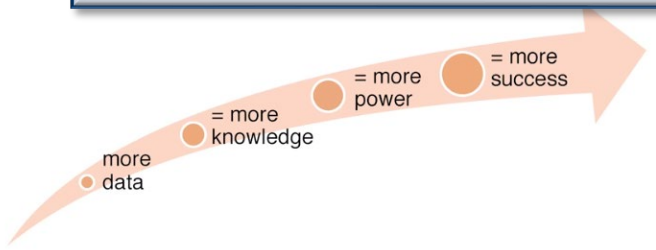
multiscale correlations in disease



network pathways for identification and validation of correlations and putative causal mechanism



Pathformer: a biological pathway informed transformer for disease diagnosis and prognosis using multi-omics data

Xiaofan Liu, Yuhuan Tao, Zilin Cai, Pengfei Bao, Hongli Ma, Kexing Li, Mengtao Li ✉, Yunping Zhu ✉, Zhi John Lu ✉ Author Notes

Bioinformatics, Volume 40, Issue 5, May 2024, btae316,

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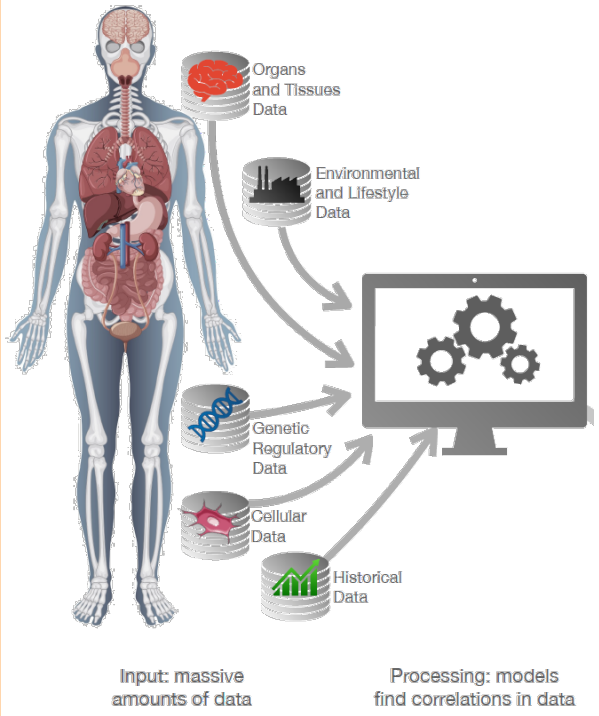

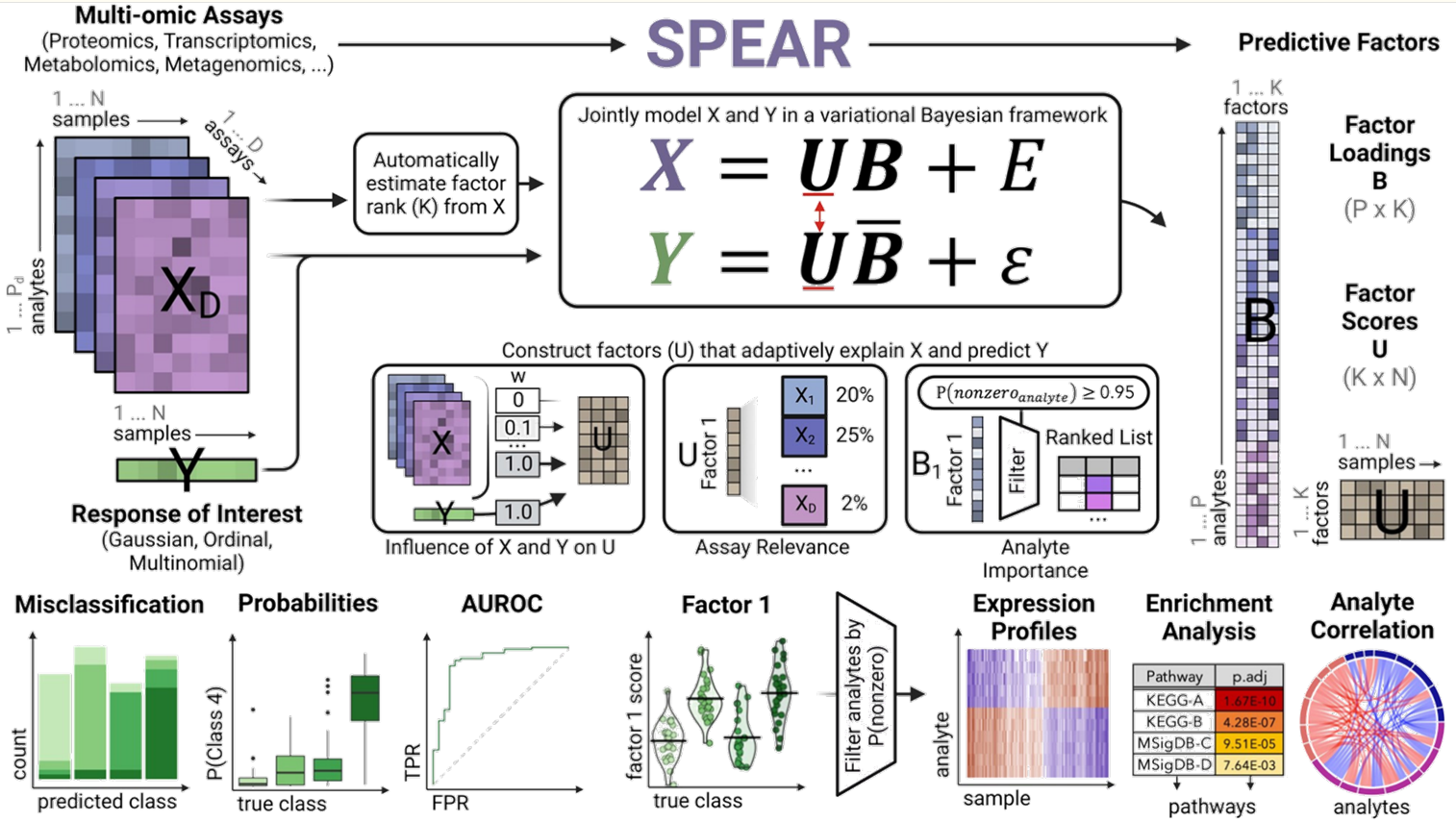

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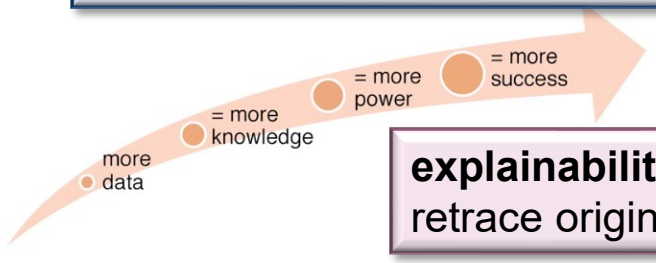

explainability is limited and not straightforward to retrace original data that explains **correlations**.

A supervised Bayesian factor model for the identification of multi-omics signatures

Jeremy P Gygi ✉, Anna Konstorum, Shrikant Pawar, Edel Aron, Steven H Kleinstein, Leying Guan ✉ Author Notes

Bioinformatics, Volume 40, Issue 5, May 2024, btae202,

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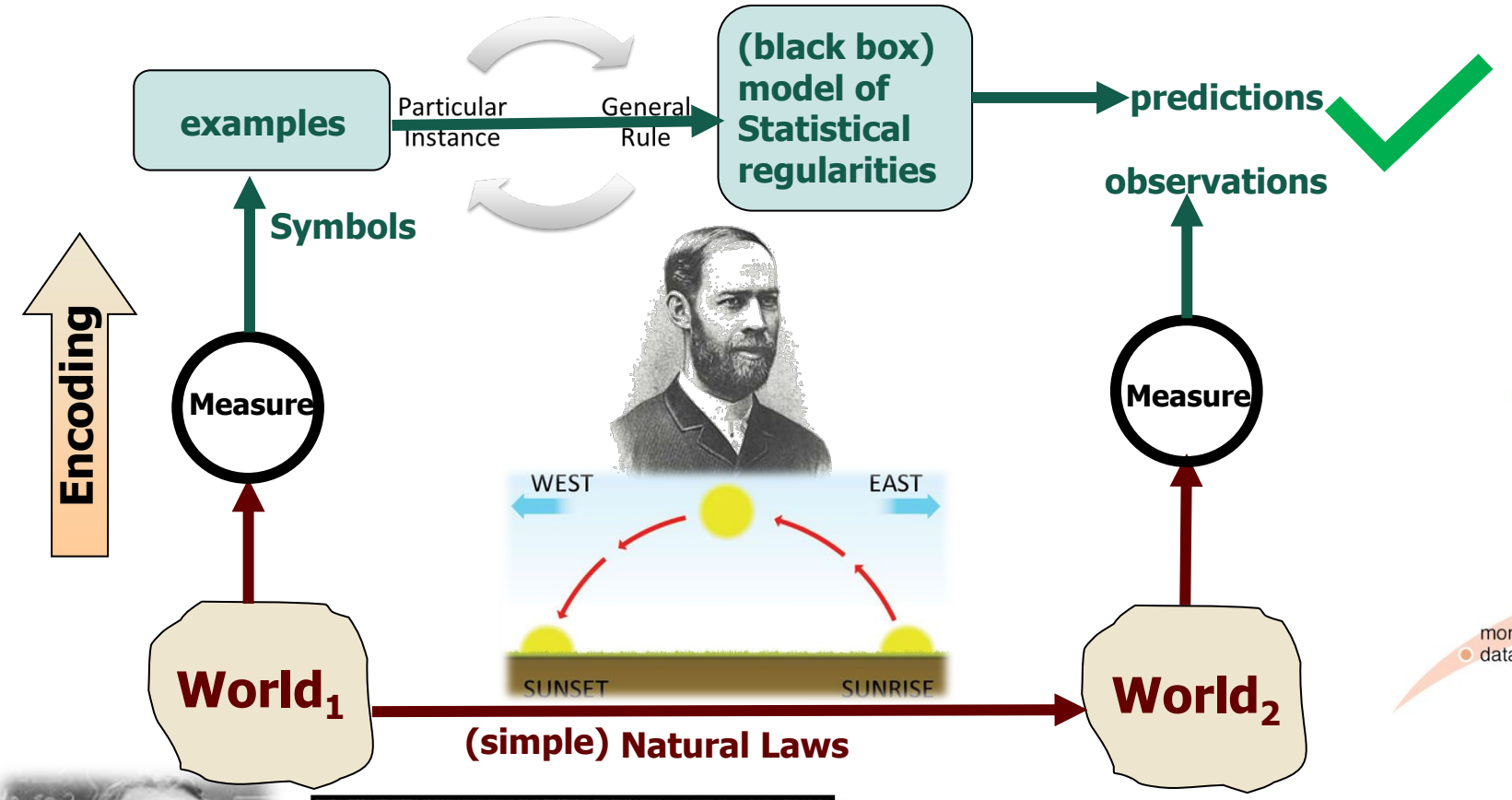
good news I & II: near-decomposability and induction



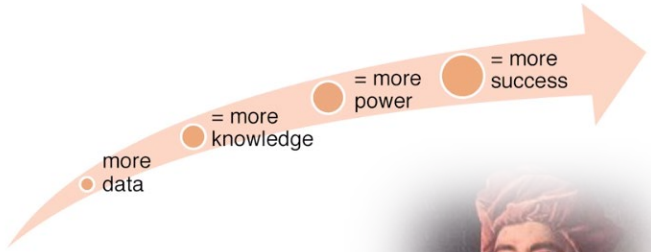
David Hume's Empiricism

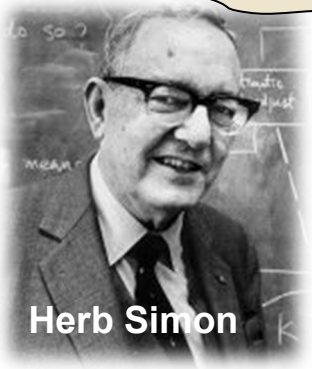
Everyday knowledge depends on patterns of repeated experience

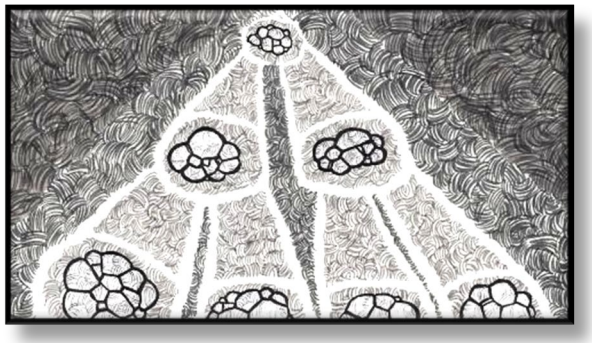
"It is not reason which is the guide of life, but custom."

"A wise man proportions his belief to the evidence"

The Magic Formula ...







Studying (multiscale, contextual) complexity possible if world is near-decomposable and predictable from past examples

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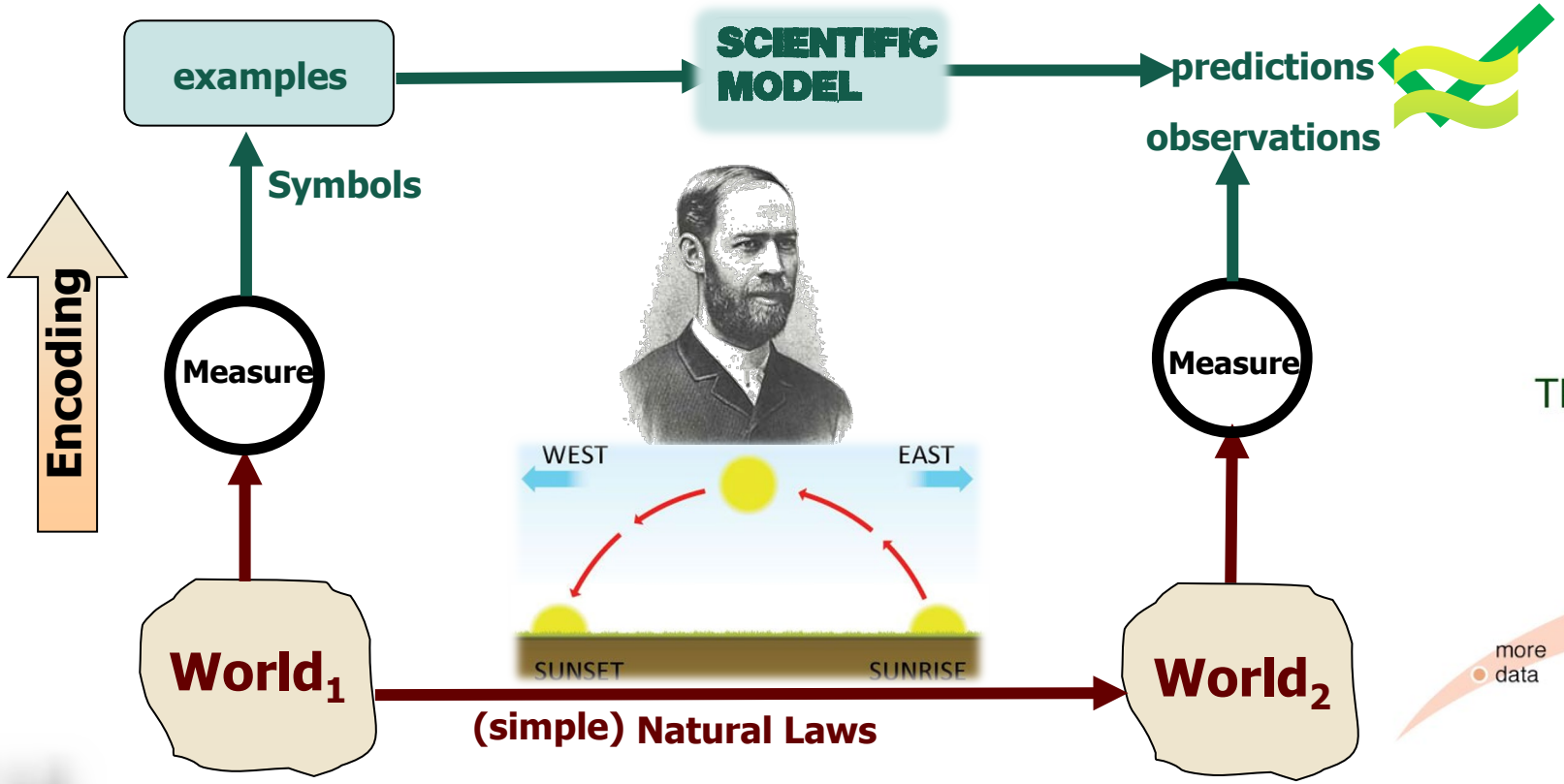
Bad news I: computational limits



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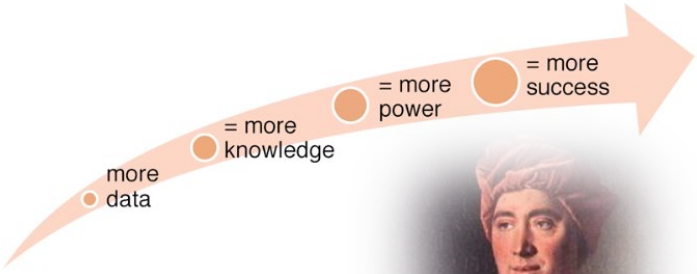


George Klir

Model complexity

We must simplify computational models

Tradeoff descriptive and uncertainty-based complexity


Hans Bremmermann

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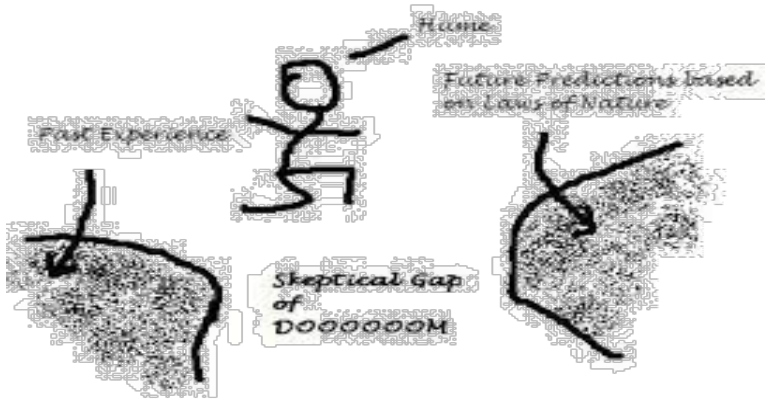
Bad news II: black swans

Bertrand Russell
On Hume's common sense practical skepticism



The Inductive Leap

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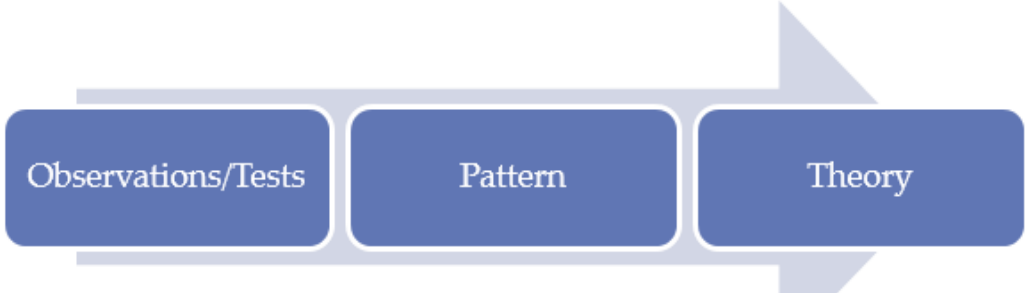

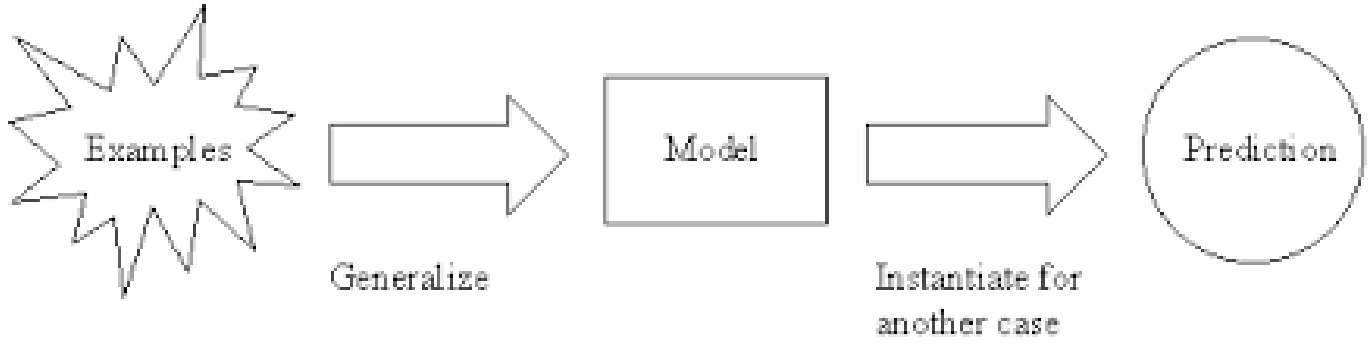

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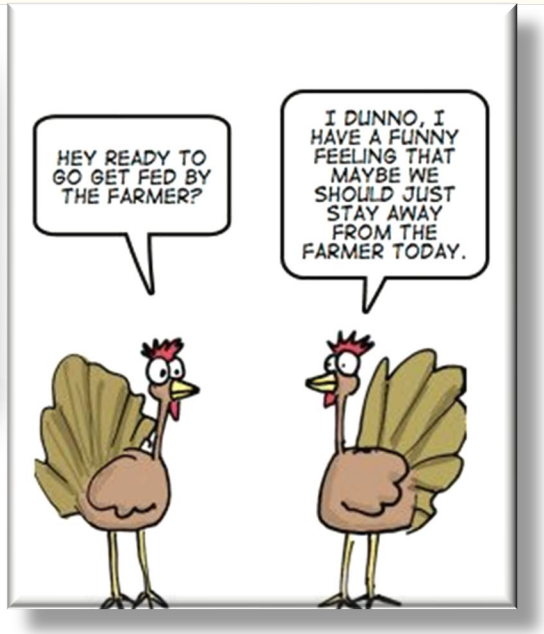

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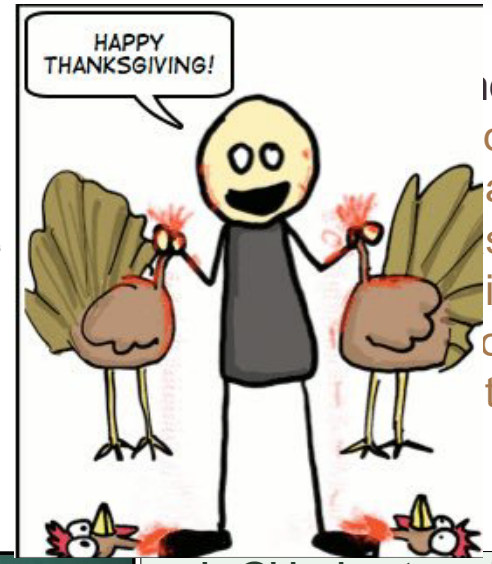

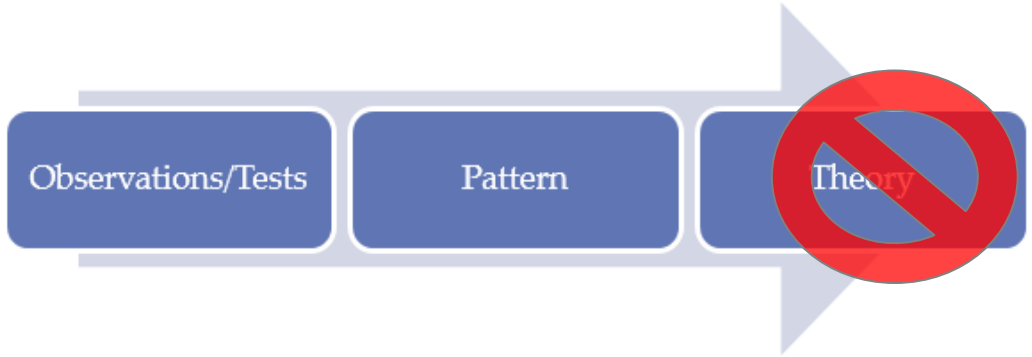

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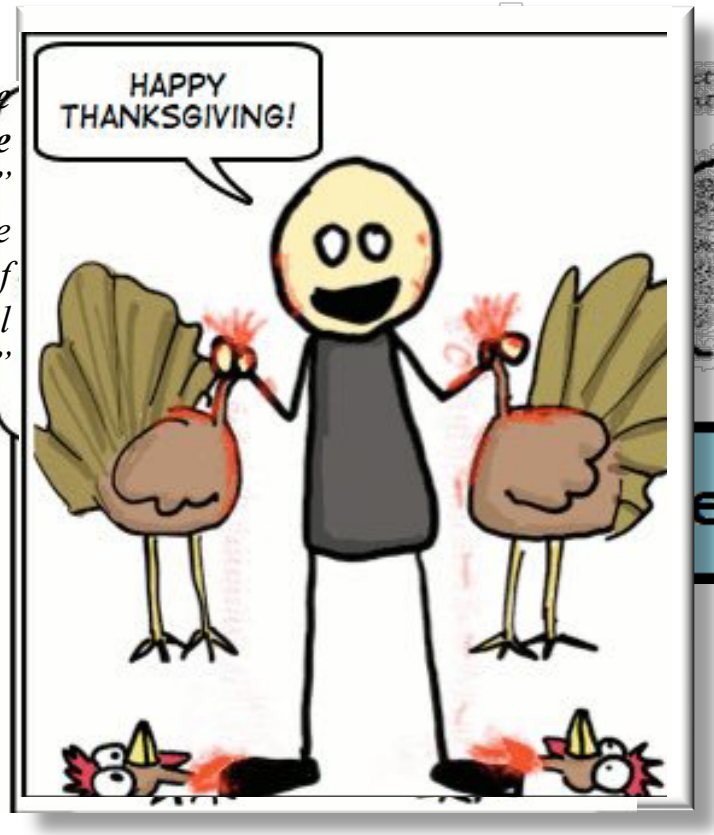
Eugene Wigner

"Every empirical law has the disquieting quality that one does not know its limitations."
E. Wigner [1957] in "The Unreasonable Effectiveness of Mathematics in the Natural Sciences"

Bertrand Russell
On Hume's common sense practical skepticism

Karl Popper's Falsification Principle
logical asymmetry between verification and falsificatic
many observations do not derive (universal) theories, single observation can falsify it: scientific theories (deduced) from induction are **testable**.



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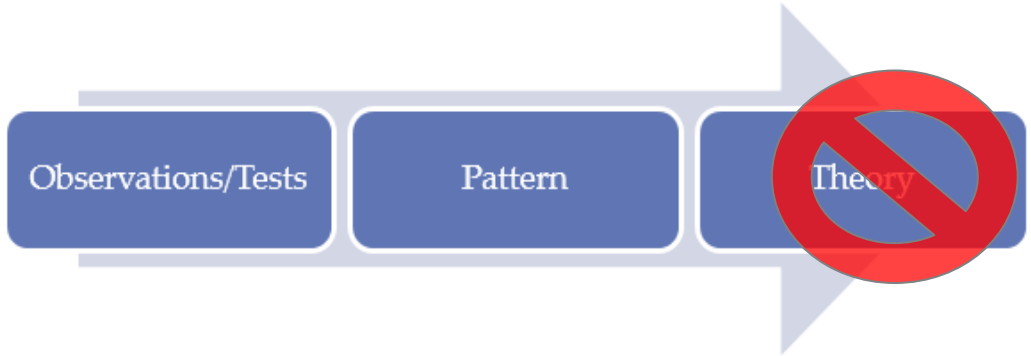

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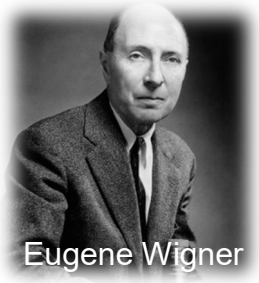
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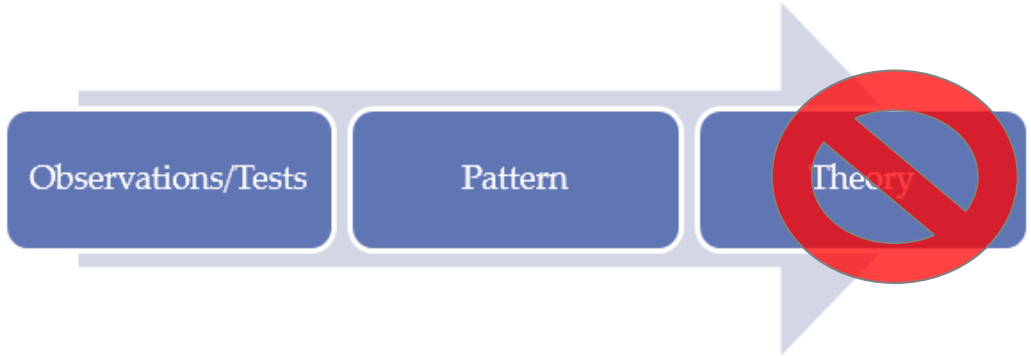

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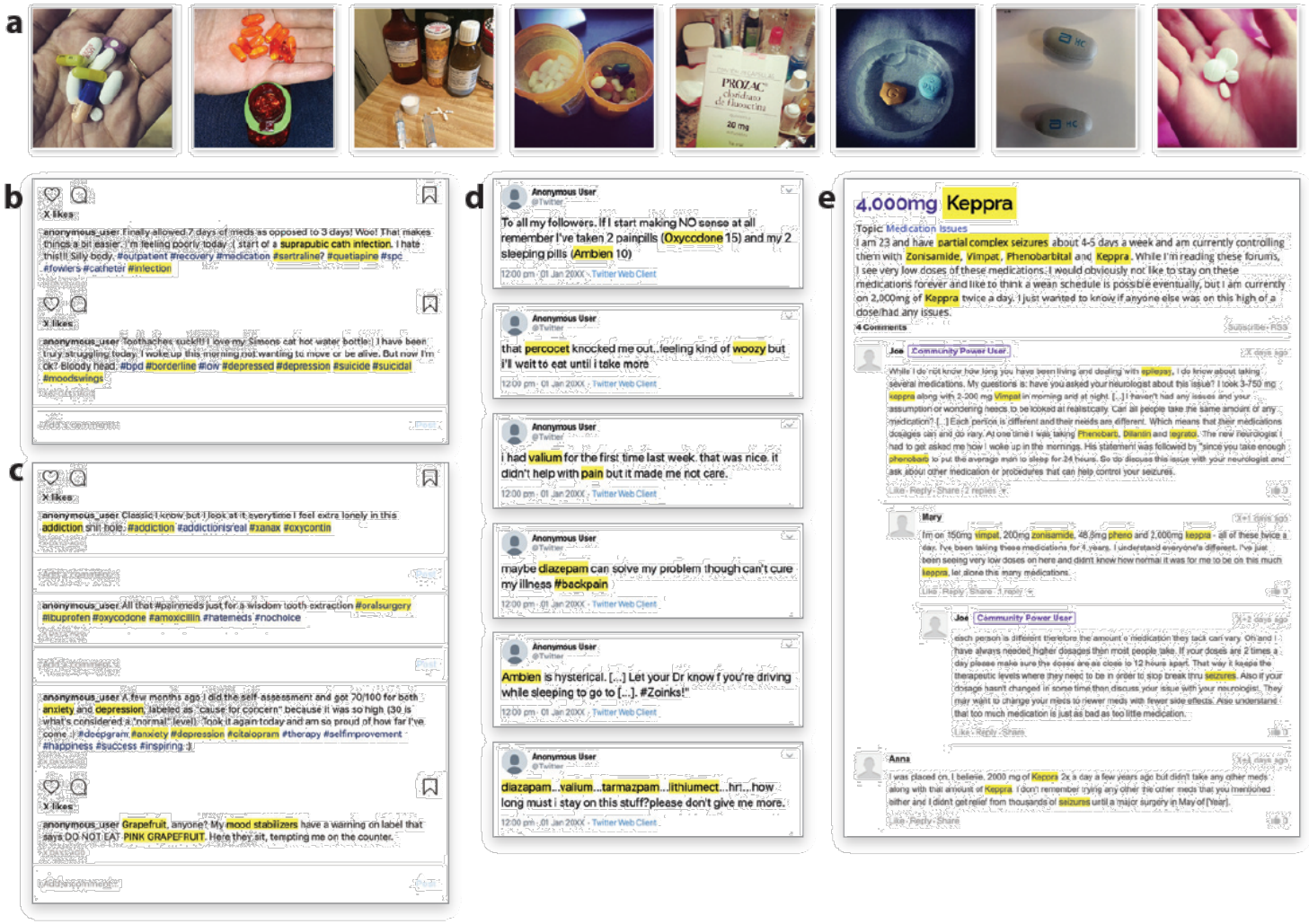
social media data pipelines for biomedicine



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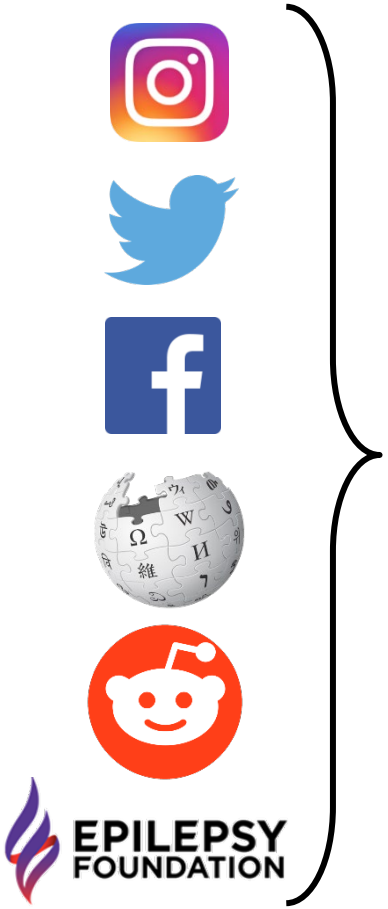

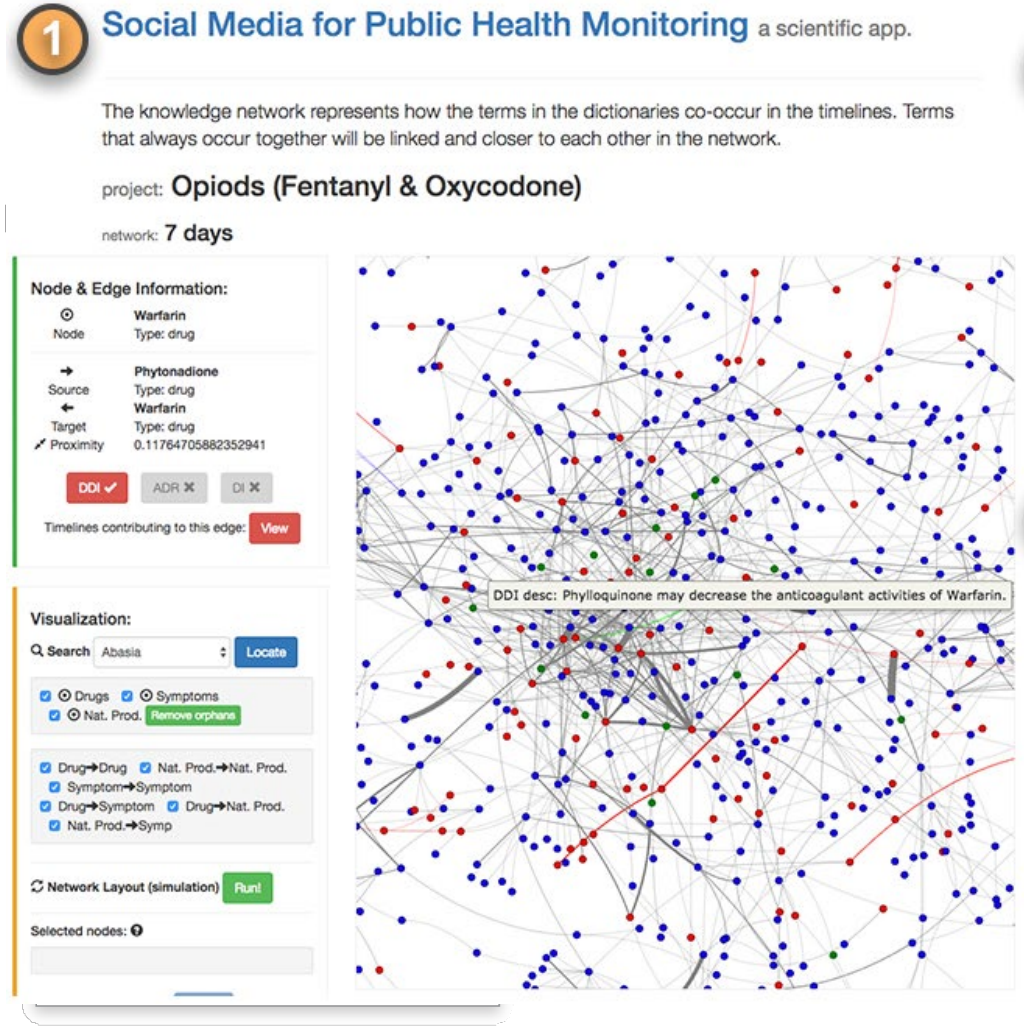

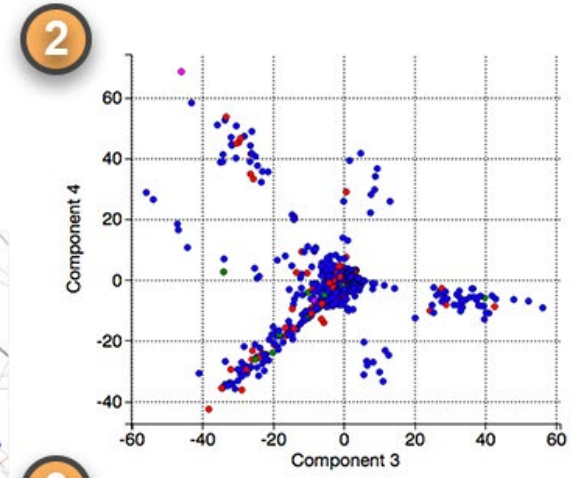

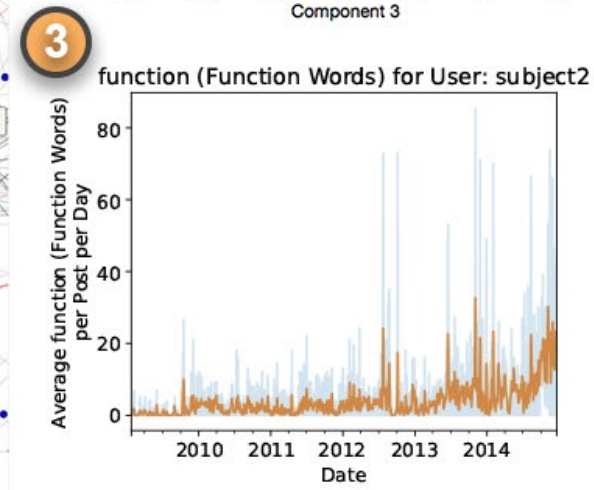

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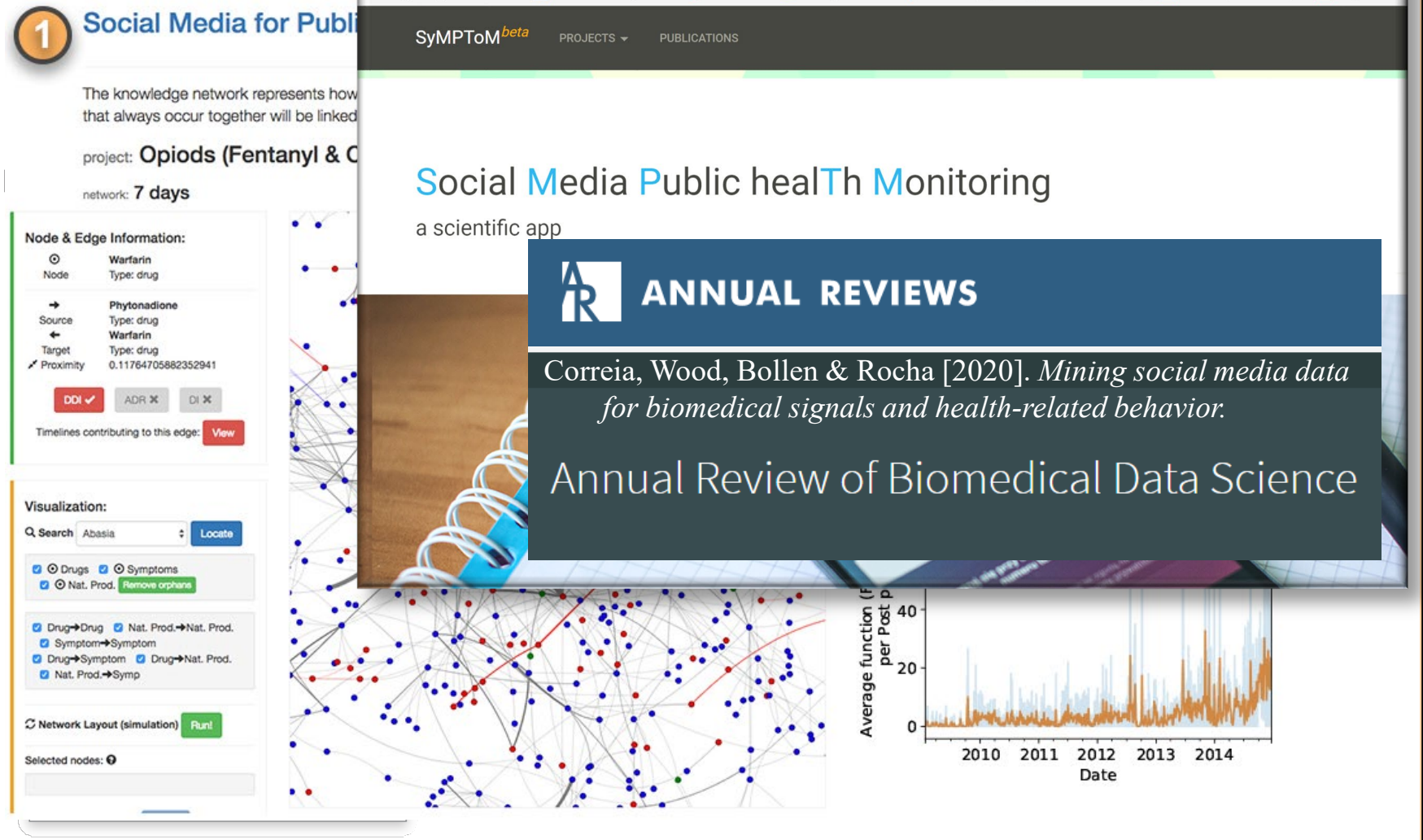

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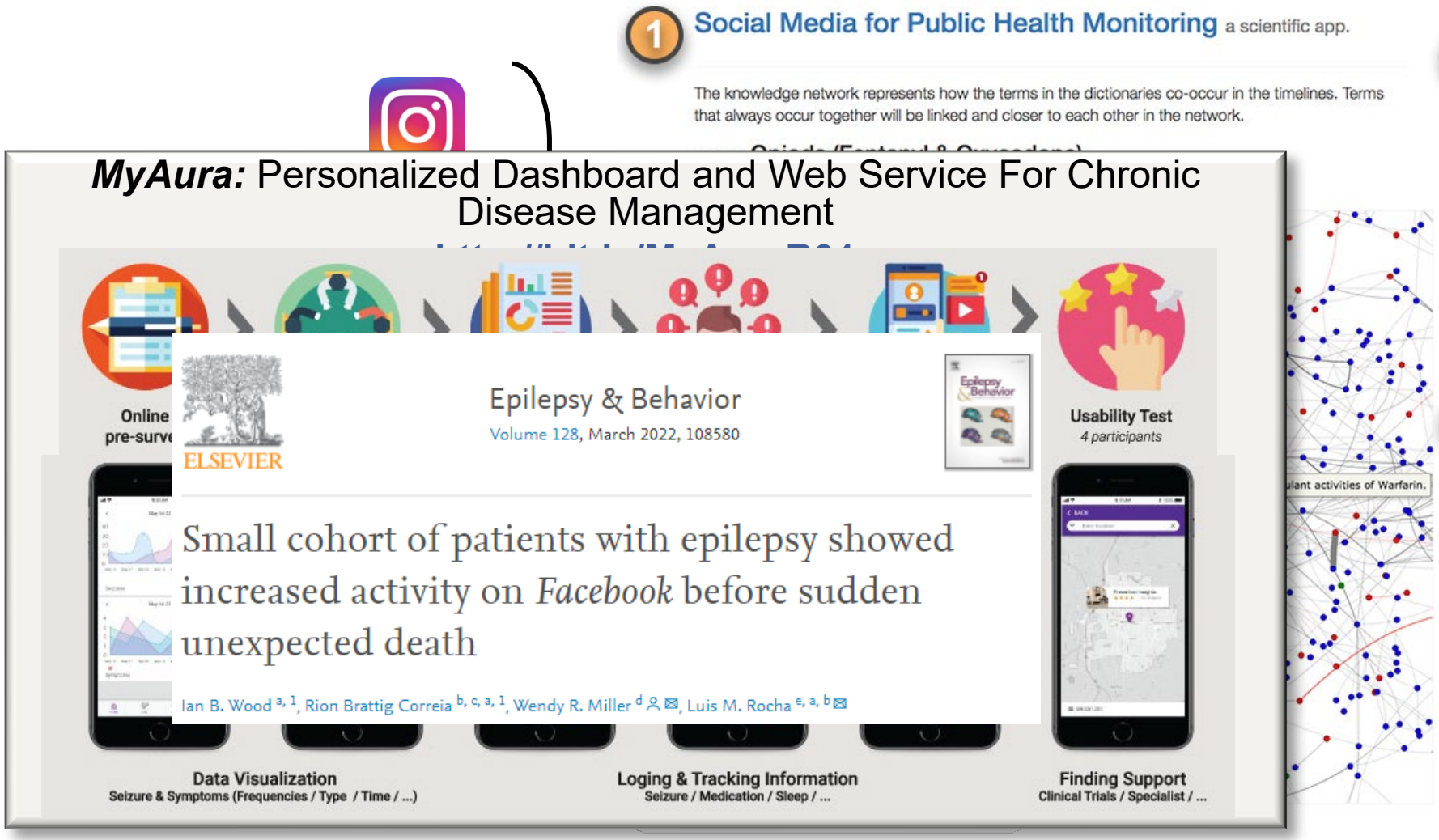

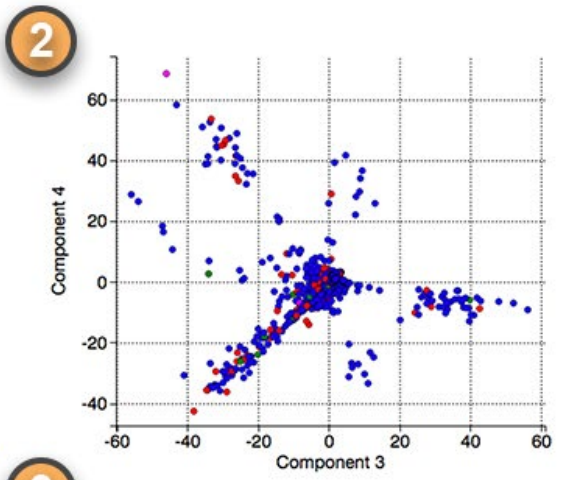

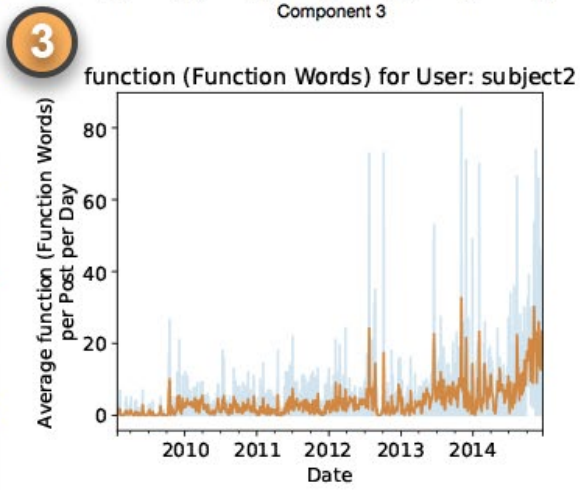

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resolving a sociobiology question on a planetary scale

- Social Media (Twitter) Mood and Web Searches
  - Understanding collective human behavior
  - Discovering mood transitions in health

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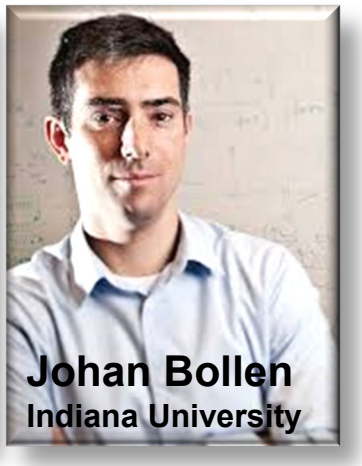
Human Sexual Cycles are Driven by Culture and Match Collective Moods

Ian B. Wood, Pedro L. Varela, Johan Bollen, Luis M. Rocha & Joana Gonçalves-Sá



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Global Patterns of Seasonal Variation in Human Fertility[a]

DAVID A. LAM[b,d] AND JEFFREY A. MIRON[c]

Emerald Article: Summer nights: A review of the evidence of seasonal variations in sexual health indicators among young people

Wendy Macdowall, Kaye Wellings, Judith Stephenson, Anna Glasier

Annual Rhythm of Human Reproduction: I. Biology, Sociology, or Both?

Till Roenneberg and Jürgen Aschoff†*

The observed annual birth cycle (in countries where there is data). Is it driven by biological adaptation or culture?

THE EFFECTS OF TEMPERATURE ON HUMAN FERTILITY*

DAVID A. LAM AND JEFFREY A. MIRON

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Western Northern countries, Canada, Denmark, Finland, France, Germany, Italy, Lithuania, Mas: Austrialta, Netherlands, Poland, Portugal, Spain, Sweden and USA

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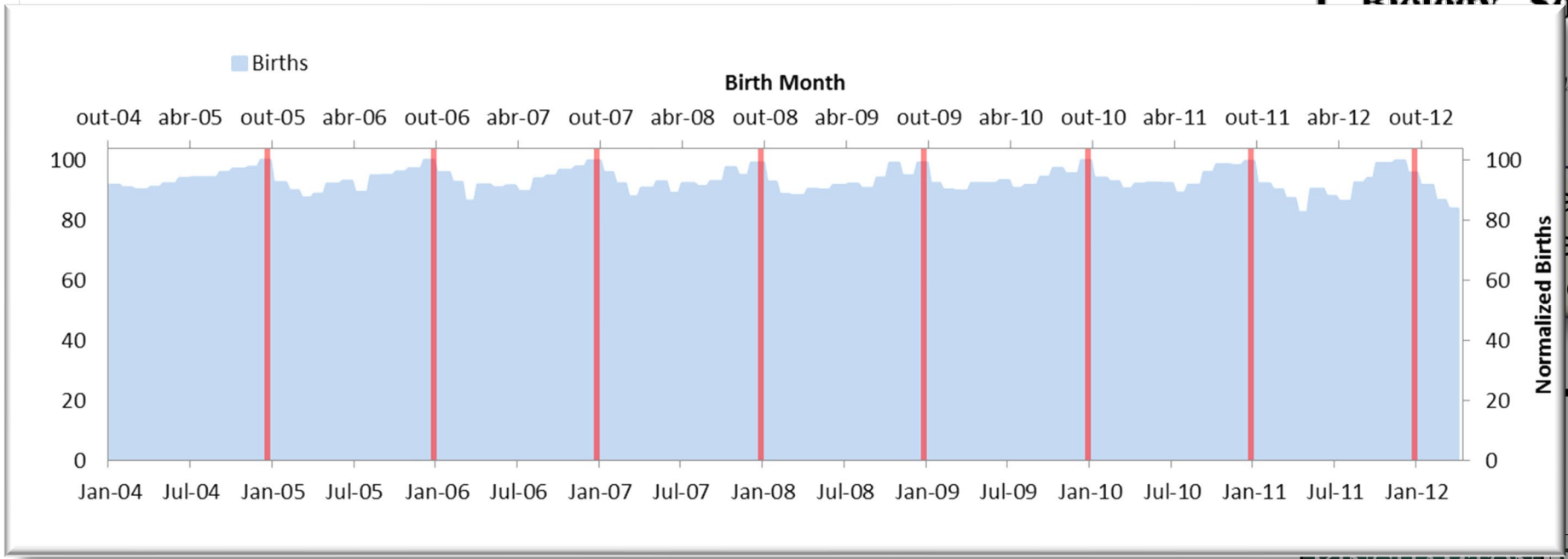

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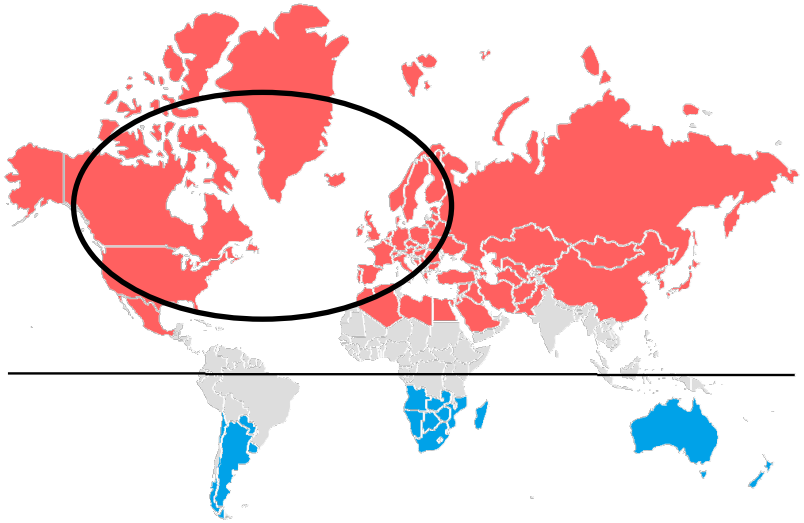
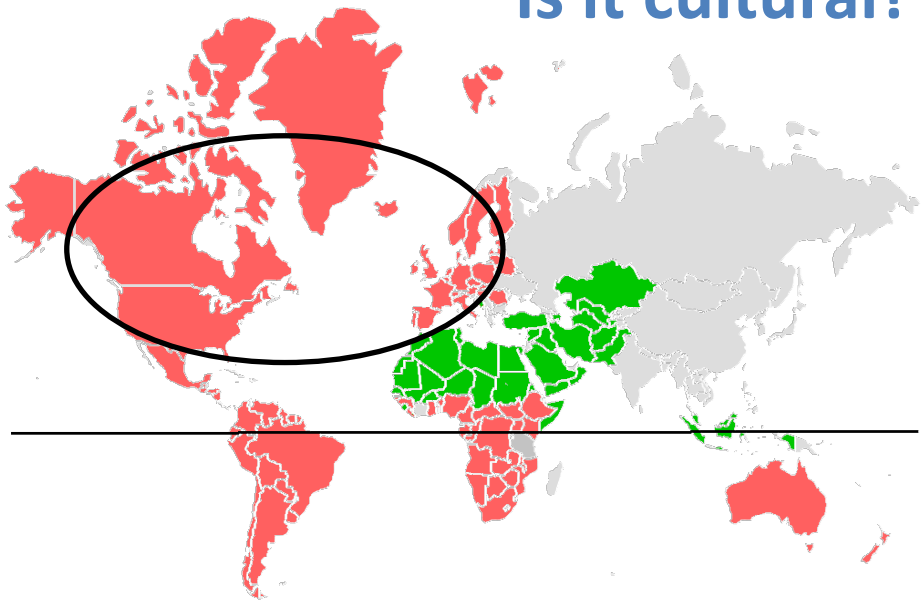
search and social media mood provide global patterns

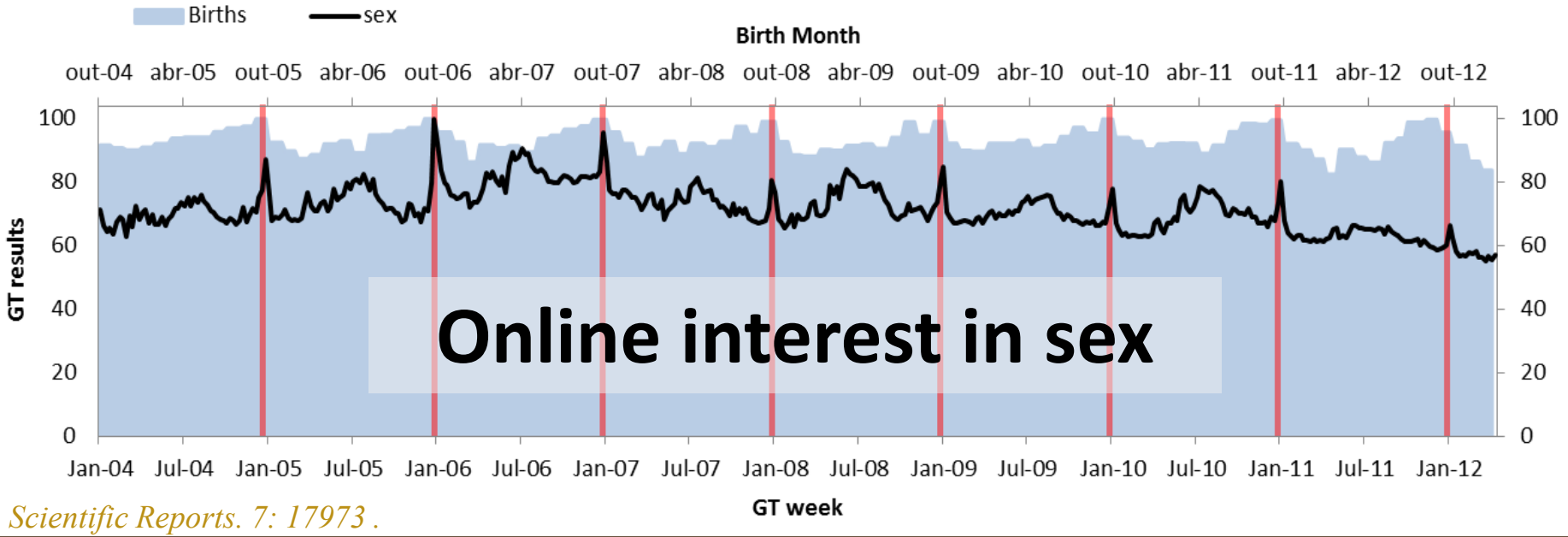
Is it biological adaptation?



Is it cultural?



Google Trends



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Hypothesis falsification in data and complexity science

resolving a sociobiology question on a planetary scale

- Social Media (Twitter) Mood and Google Searches
  - Understanding collective human behavior
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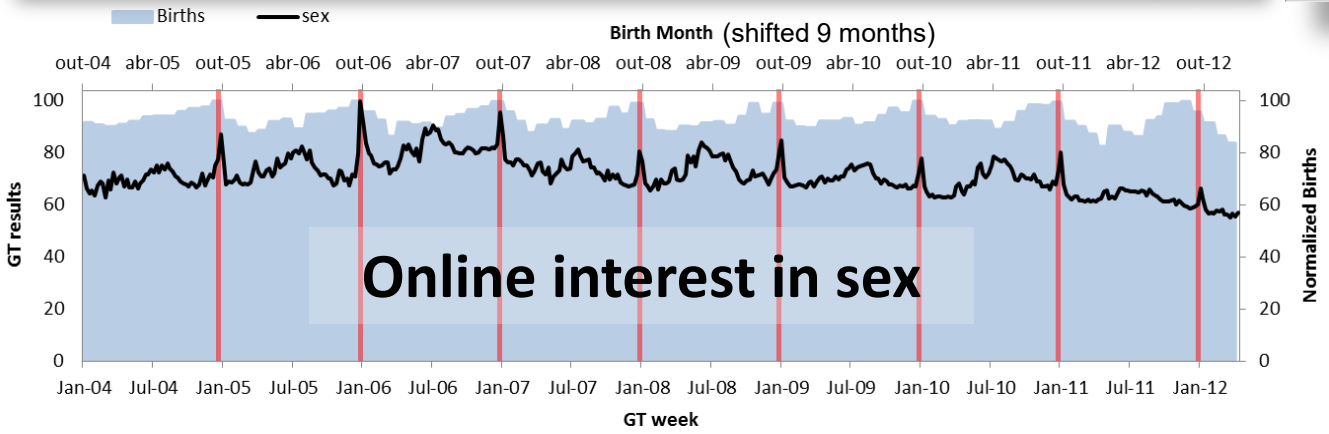
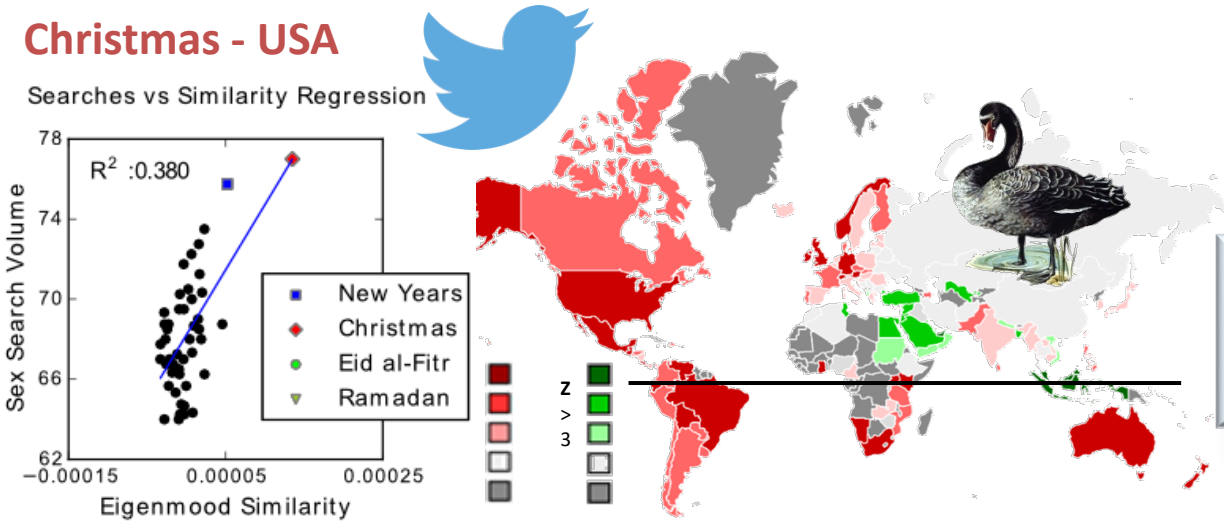
Sex search patterns (proxy for interest in sex and births) are **culturally-driven** and correlate with distinct **mood patterns** on social media



Why? child-centered and gift-giving holidays?



granger causality analysis suggests that mood causes interest in sex

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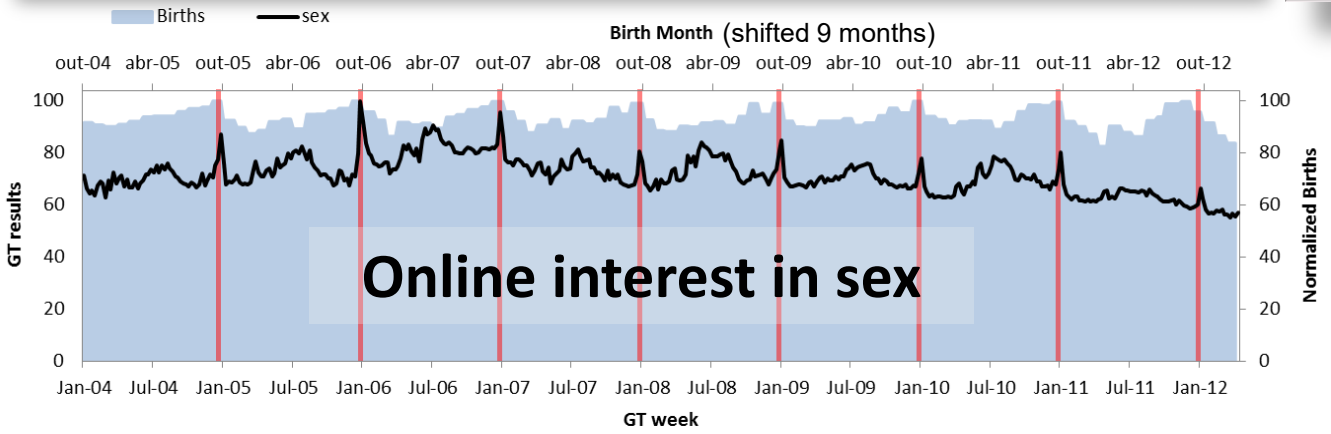
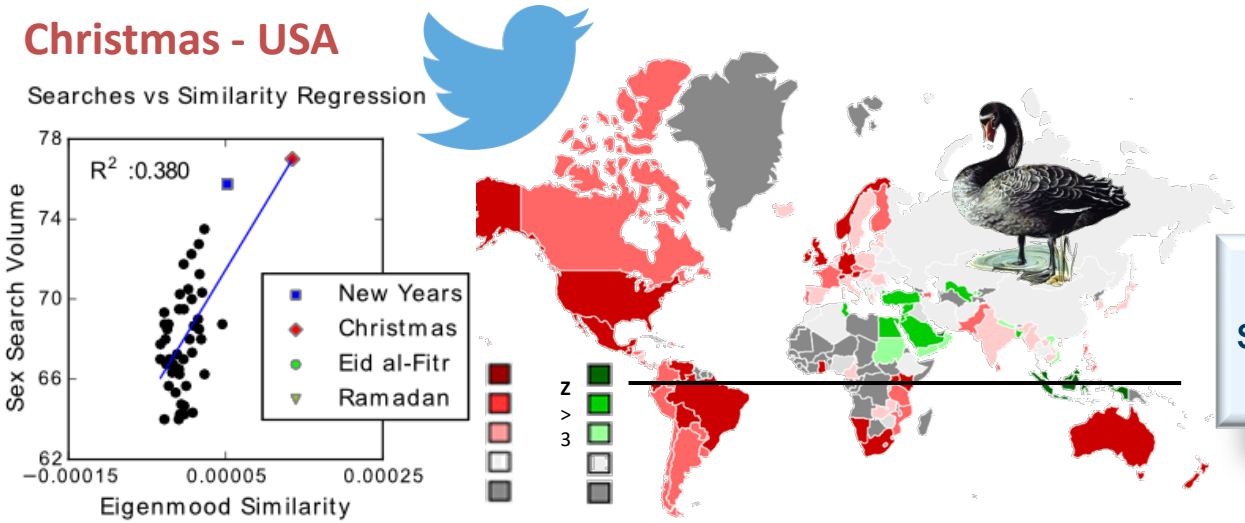
Wood, Varela, Bollen, Rocha & Sá [2017]. *Scientific Reports. 7: 17973 .*

Hypothesis falsification in data and complexity science

resolving a sociobiology question on a planetary scale

- Social Media (Twitter) Mood and Google Searches
  - Understanding collective human behavior
  - Discovering mood transitions in health





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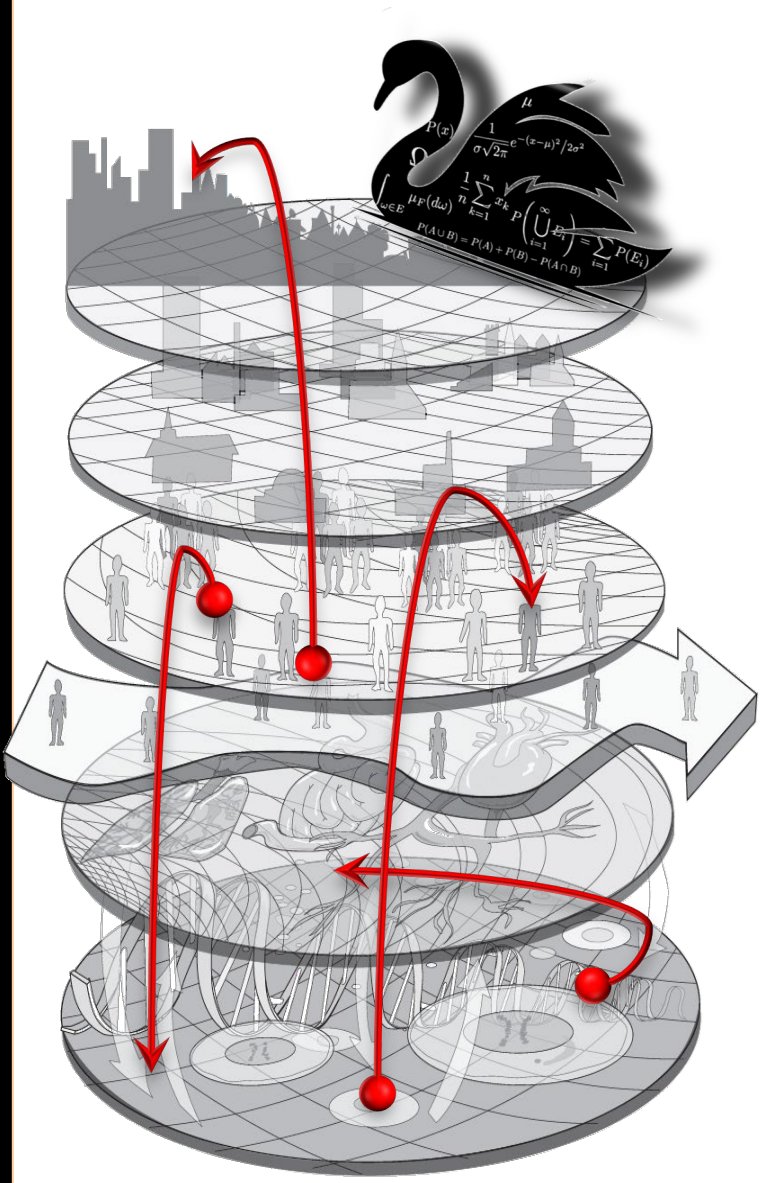
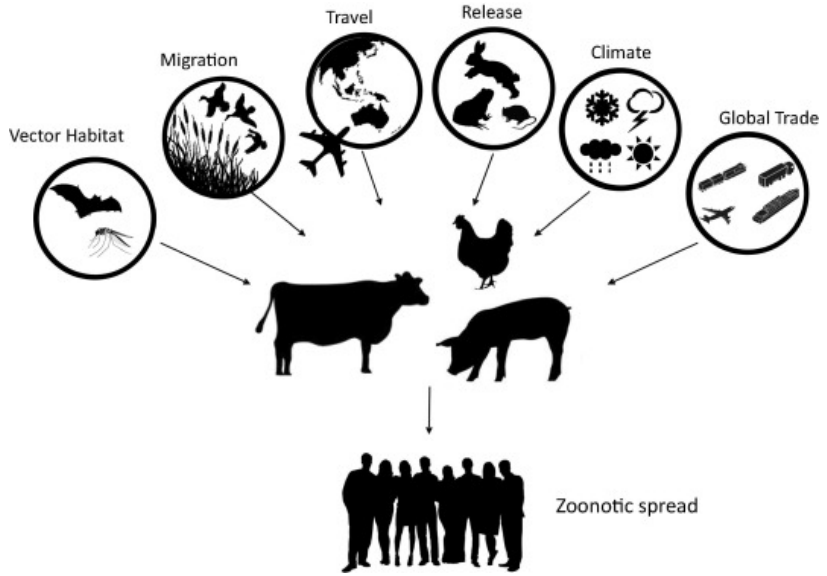
Bad news III: inductive, “boxed” model failure with complex systems





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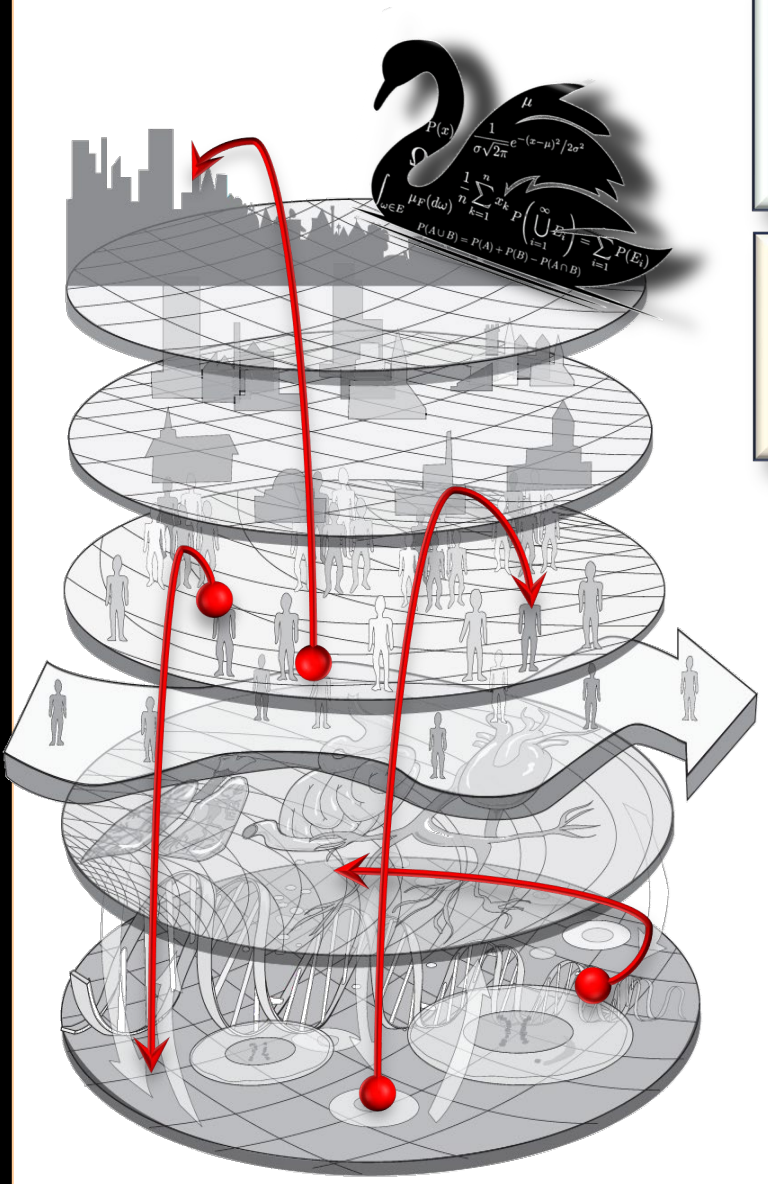
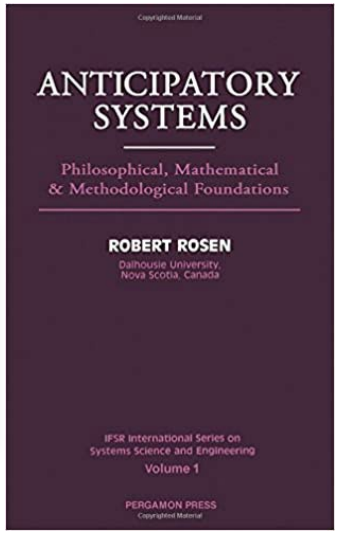
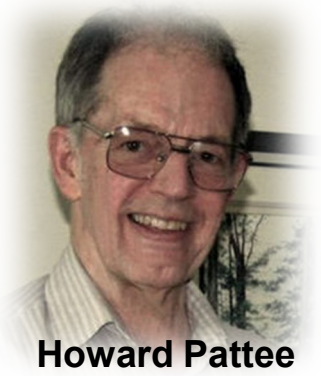


Key insight: complex systems need multi-level, contextual/actionable **models and theory** to predict rare, major transitions (not predictable by empirical evidence from single layer)

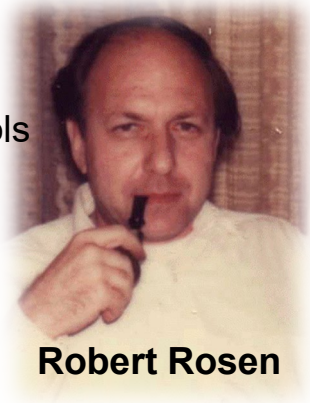
Key insight: complex systems are: 1) not reducible to self-contained multivariate structure or dynamics (boxed mechanisms), 2) not predictable from past data when it matters.



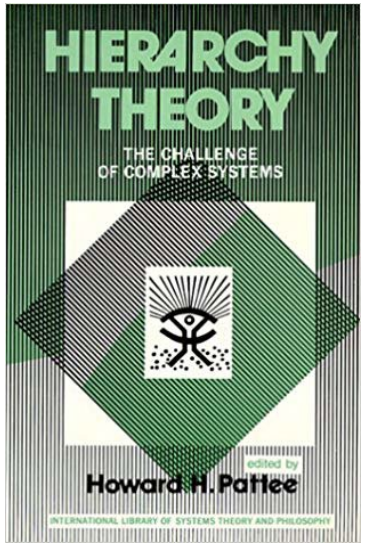


Howard Pattee

A model of any complex system will deviate as emergent properties arise from (rare) external controls



Robert Rosen



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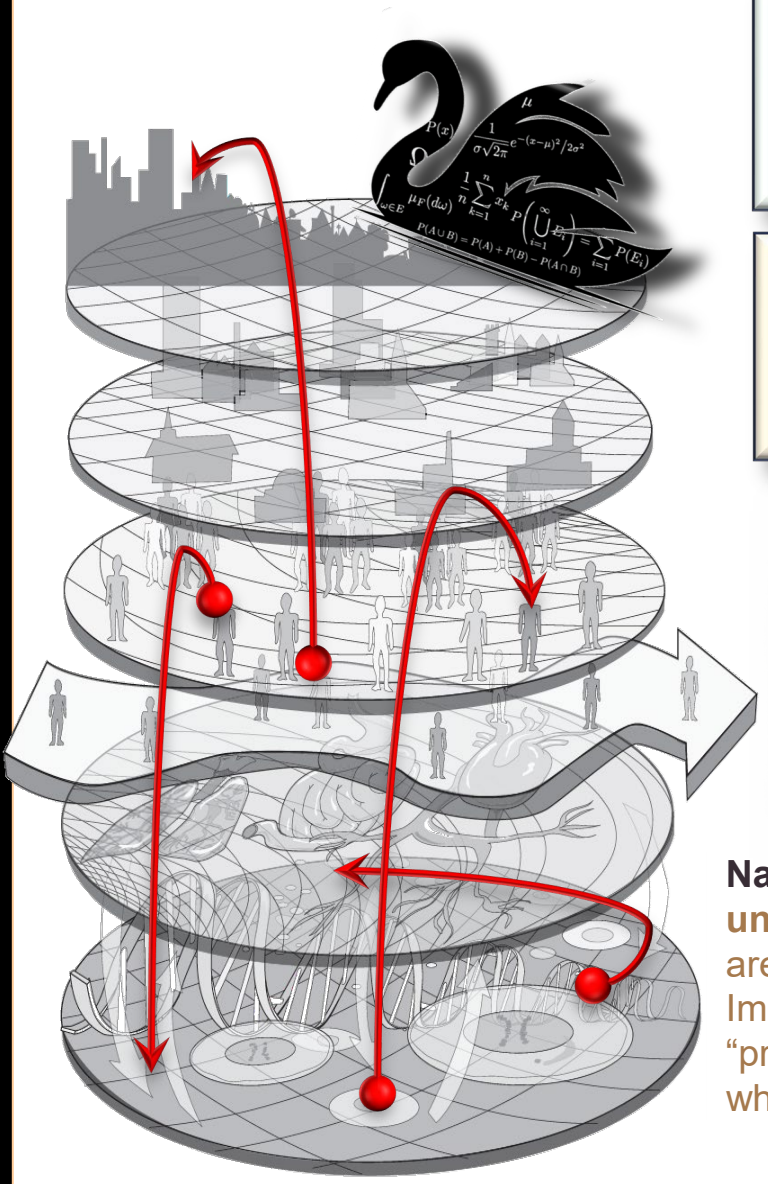

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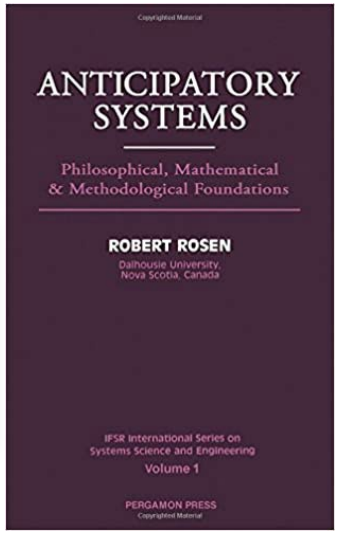
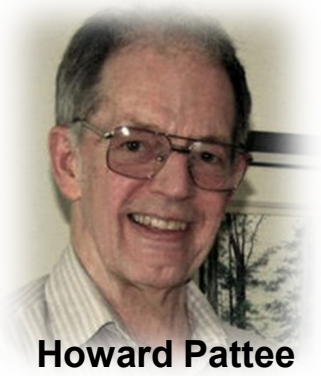
Nassim Nicholas Taleb

unexpected events of large magnitude and consequence are dominant in history.

Importance of studying robustness/resilience/evolvability

"predictions of events **depend** more and more **on theories** when their probability is small and system is **complex**"





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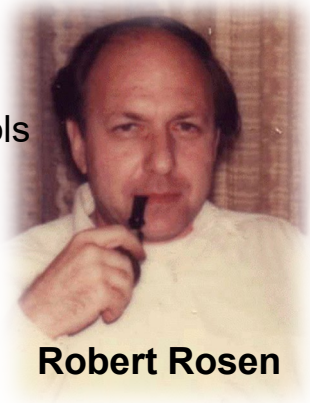

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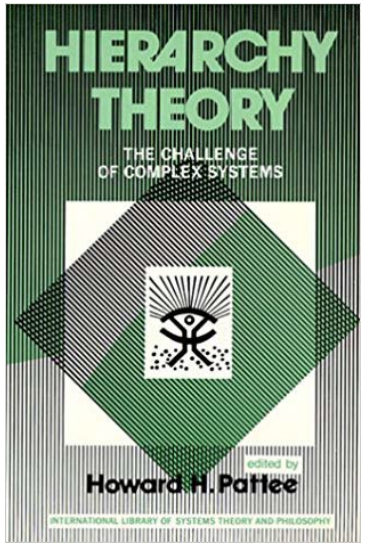

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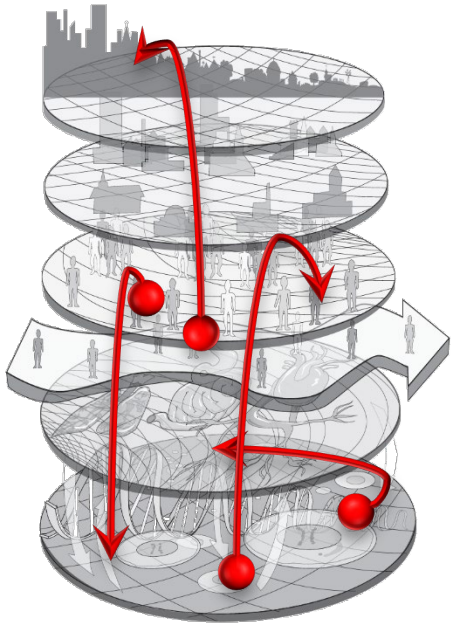
inductive models can be falsified but cannot predict black swans



examples

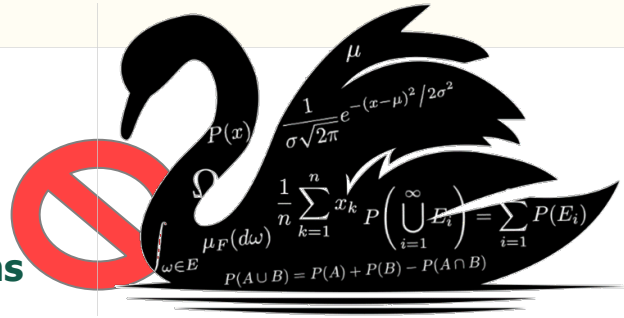
Particular Instance

General Rule

(black box) model of Statistical regularities

predictions

observations



Symbols

Encoding

Measure

Measure

$World_1$

$World_2$

Complex Natural Laws

Nassim Nicholas Taleb

Howard Pattee

Robert Rosen

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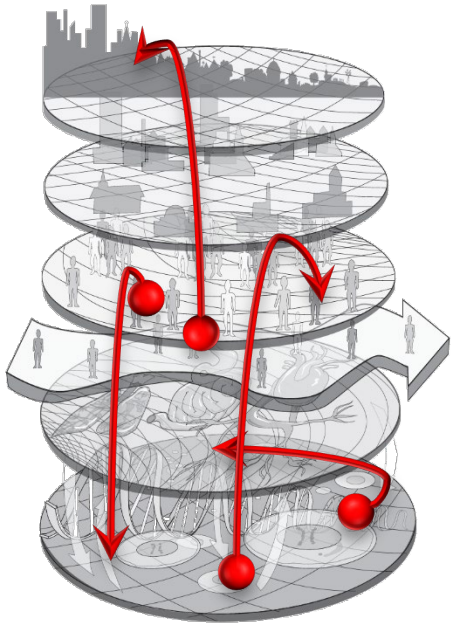

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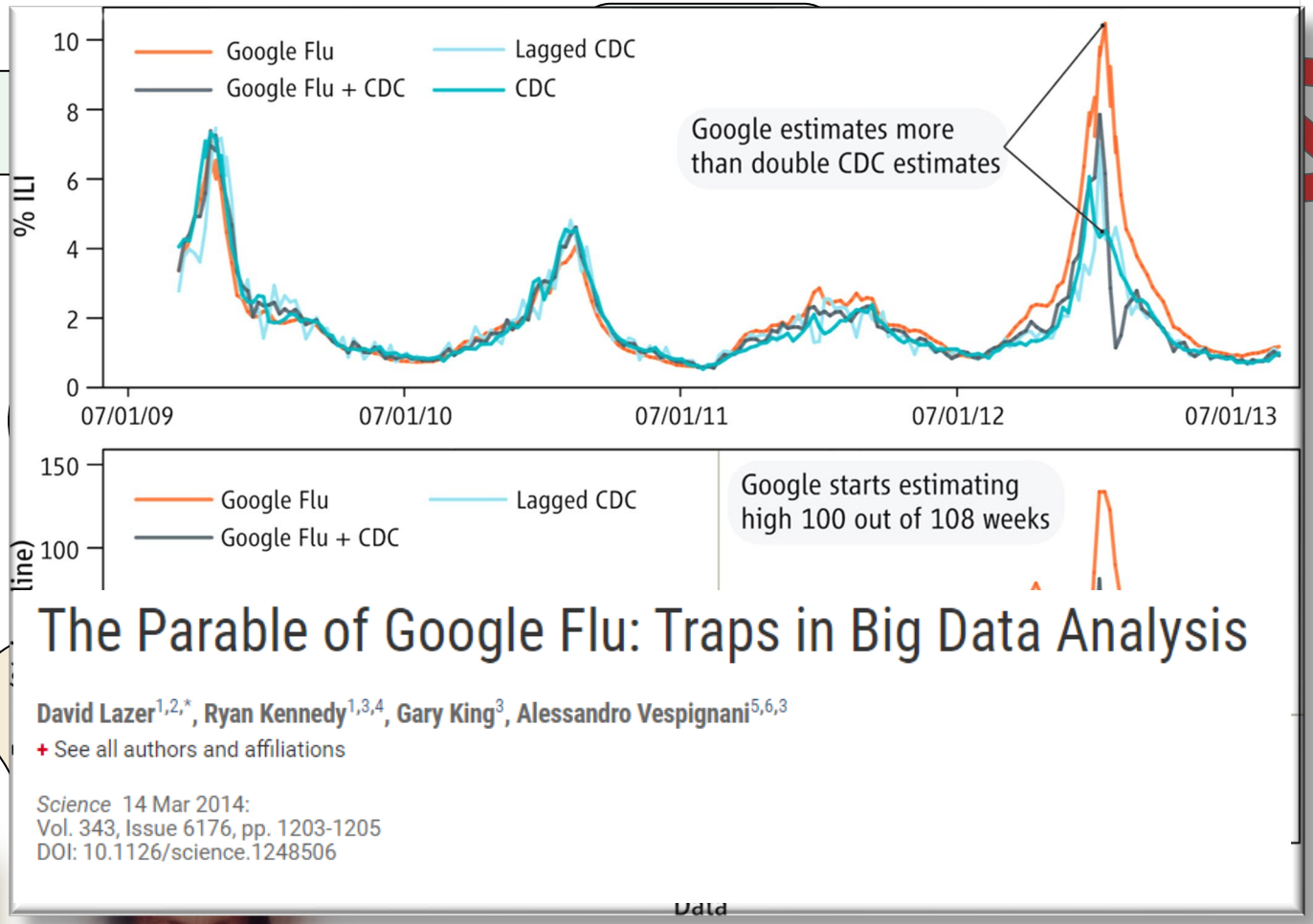
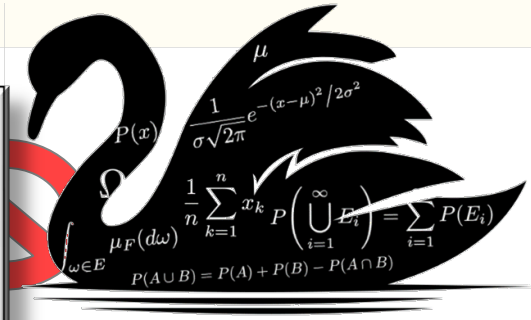


The Parable of Google Flu: Traps in Big Data Analysis

David Lazer[1,2,*], Ryan Kennedy[1,3,4], Gary King[3], Alessandro Vespignani[5,6,3]

+ See all authors and affiliations

Science 14 Mar 2014:
Vol. 343, Issue 6176, pp. 1203-1205
DOI: 10.1126/science.1248506



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machine learning depends on training data that is contextual

Angwin, Larson, Mattu & Kirchner, “Machine Bias”. *ProPublica*, May 23, 2016
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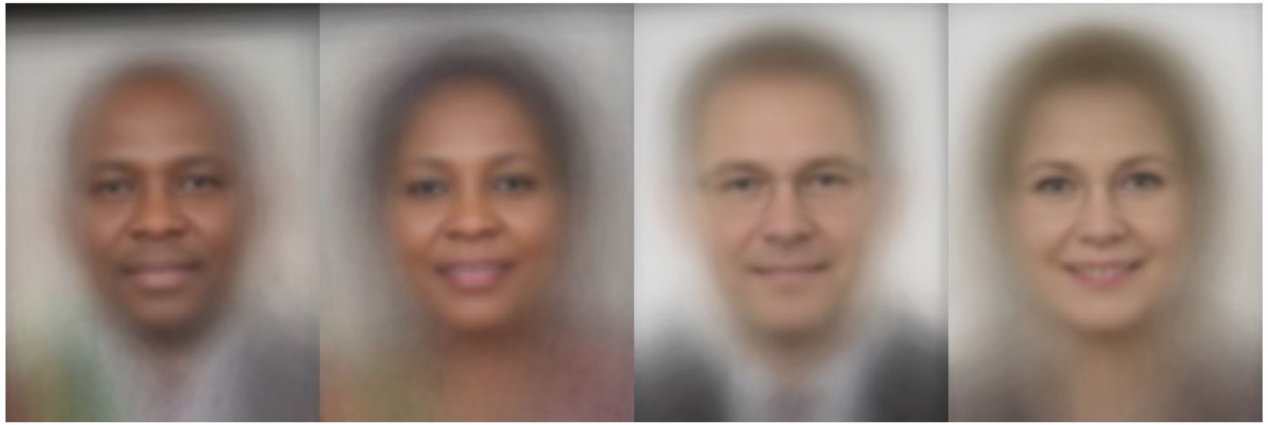
machine learning depends on training data that is contextual

Gender Classifier	Darker Male	Darker Female	Lighter Male	Lighter Female	Largest Gap
Microsoft	94.0%	79.2%	100%	98.3%	20.8%
FACE++	99.3%	65.5%	99.2%	94.0%	33.8%
IBM	88.0%	65.3%	99.7%	92.9%	34.4%



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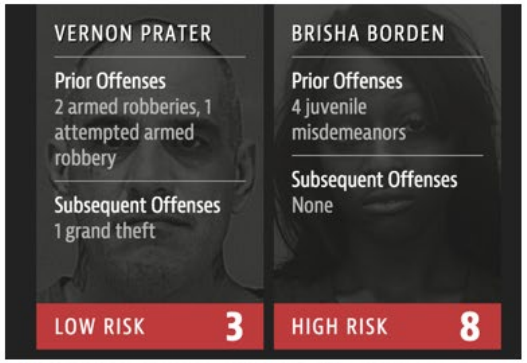

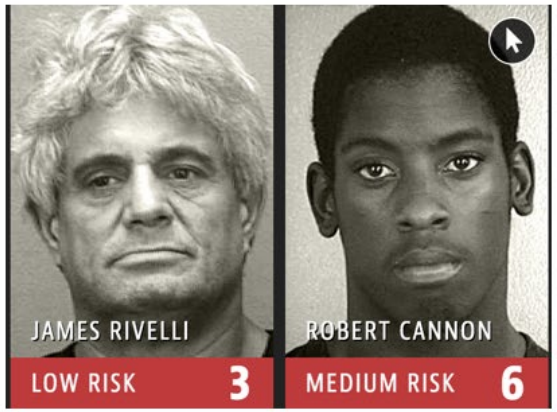

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Comparing 3 distinct health systems

Indianapolis (private)
1,228 unique *DrugBank* IDs dispensed to **264,607** patients during **2 years** (Jan 2017–Dec 2018).

Blumenau (public, free)
140 unique *DrugBank* IDs dispensed to **133,047** patients during **18 months** (Jan 2014–Jun 2015).

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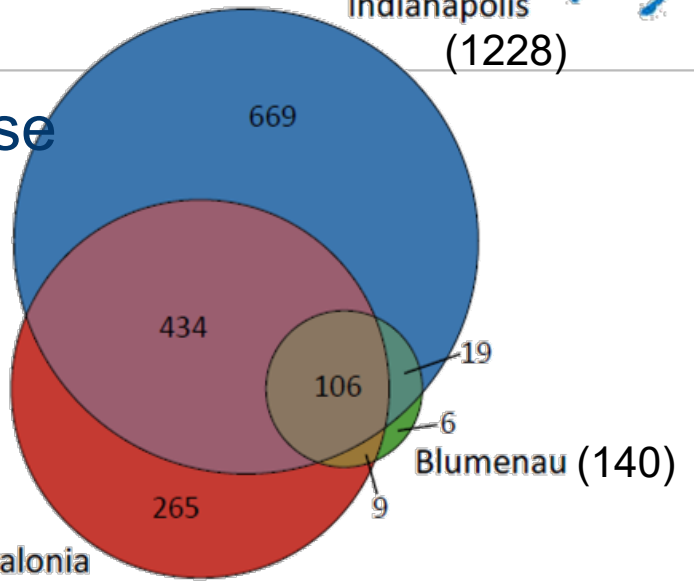
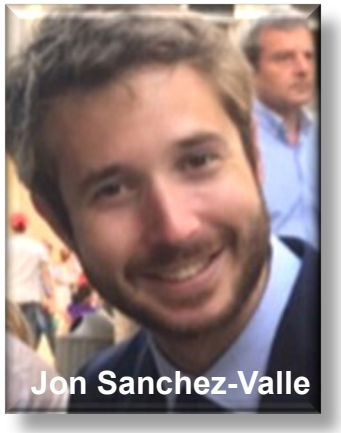
drug universe





Sanchez-Valle et al [2024].. *BMC Medicine* **22**: 166.
Correia, Araujo, Mattos, Wild & Rocha [2019]. *NPJ Digital Medicine*. 2:74.

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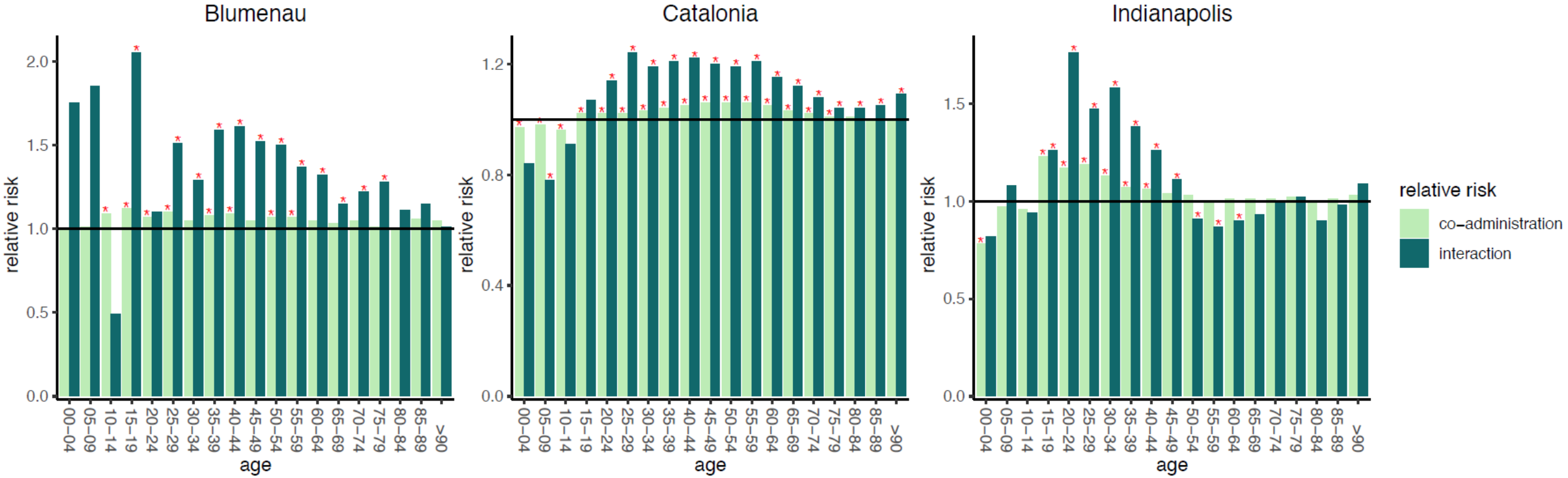
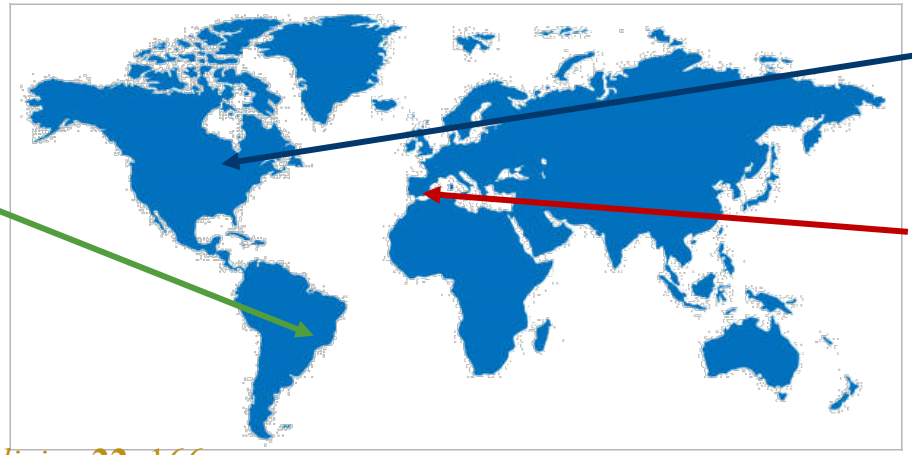
gender and age biases in drug-drug interactions





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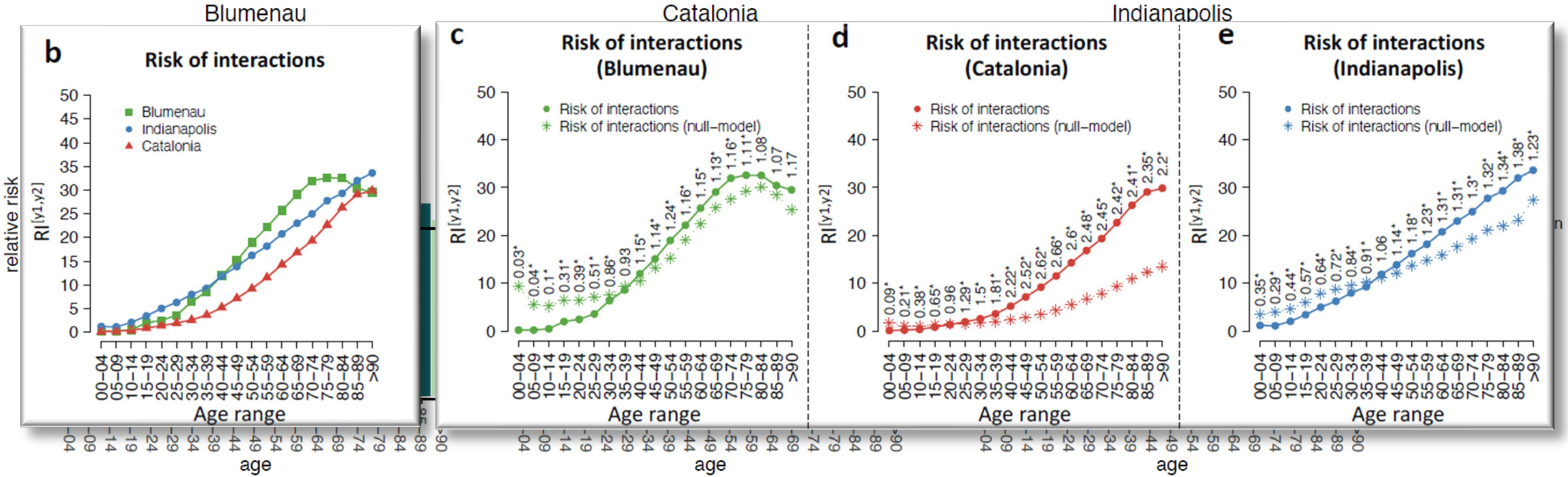

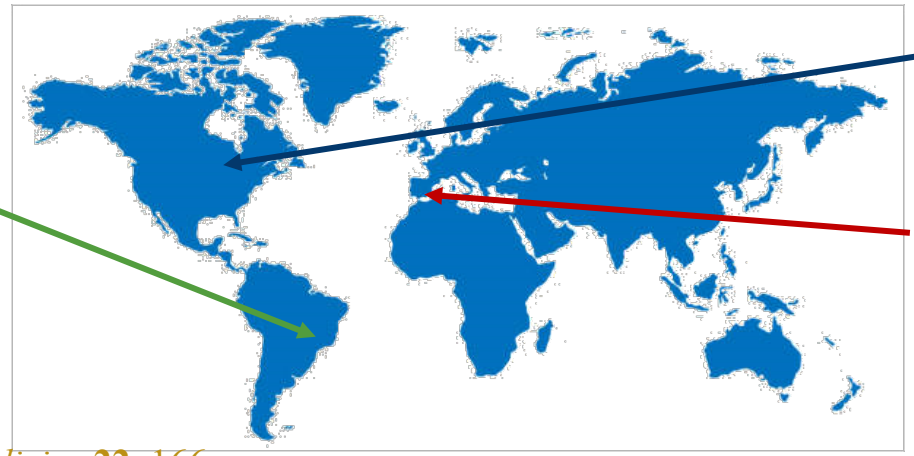

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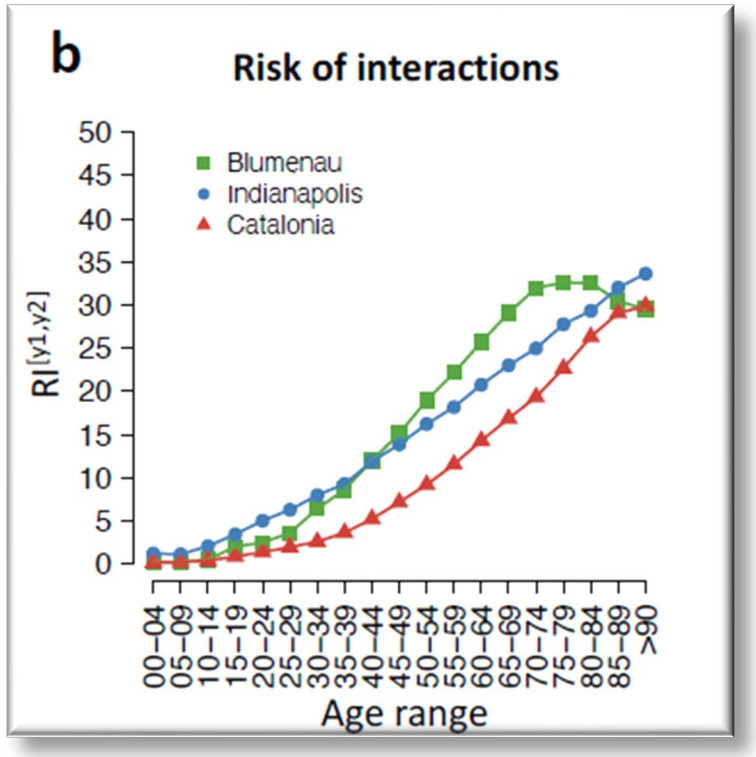

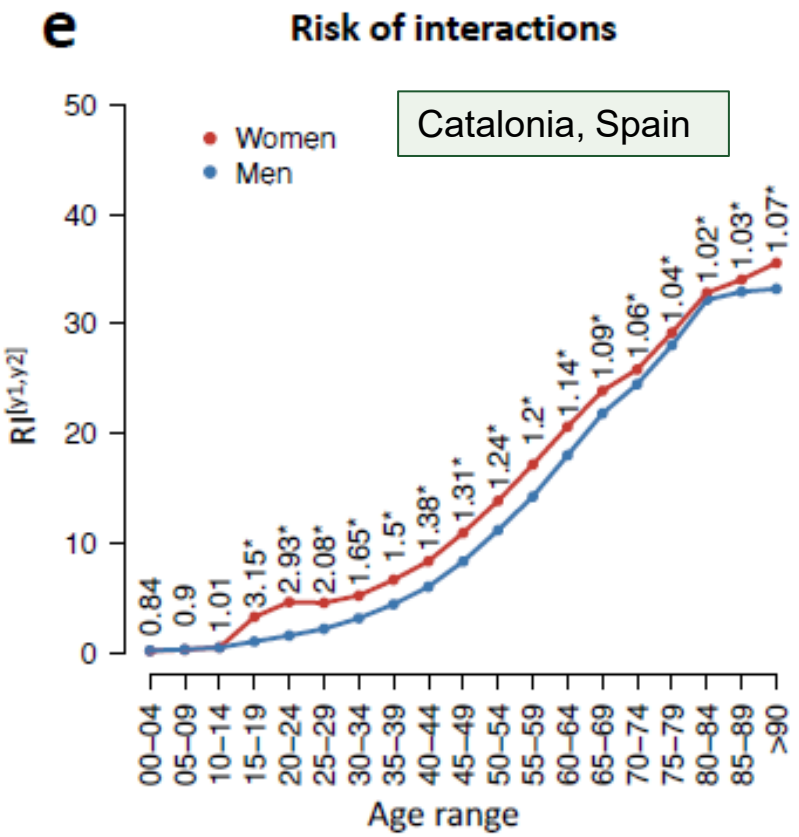

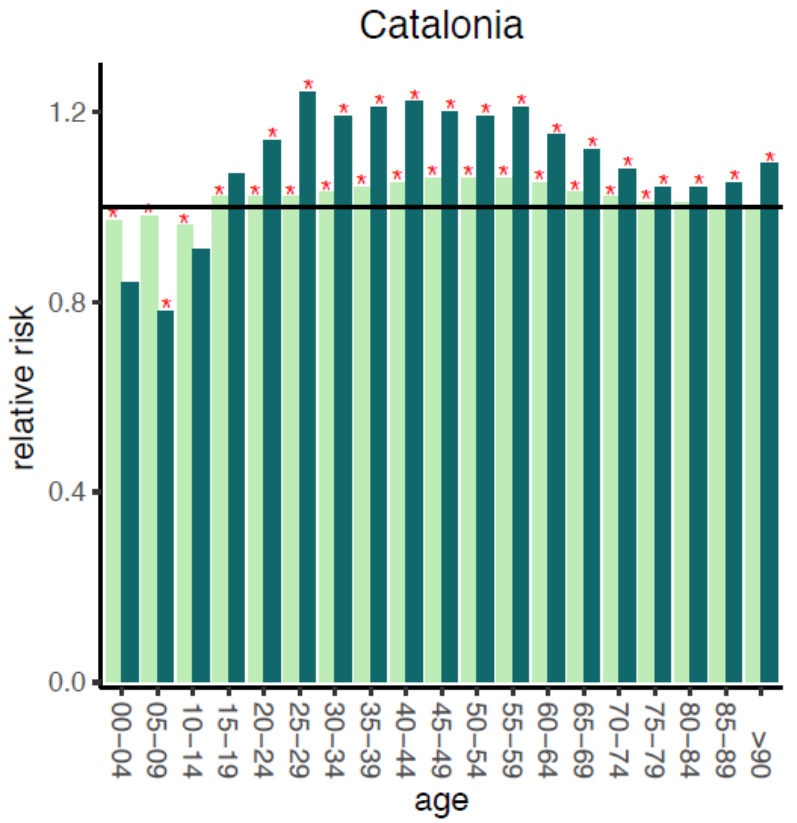

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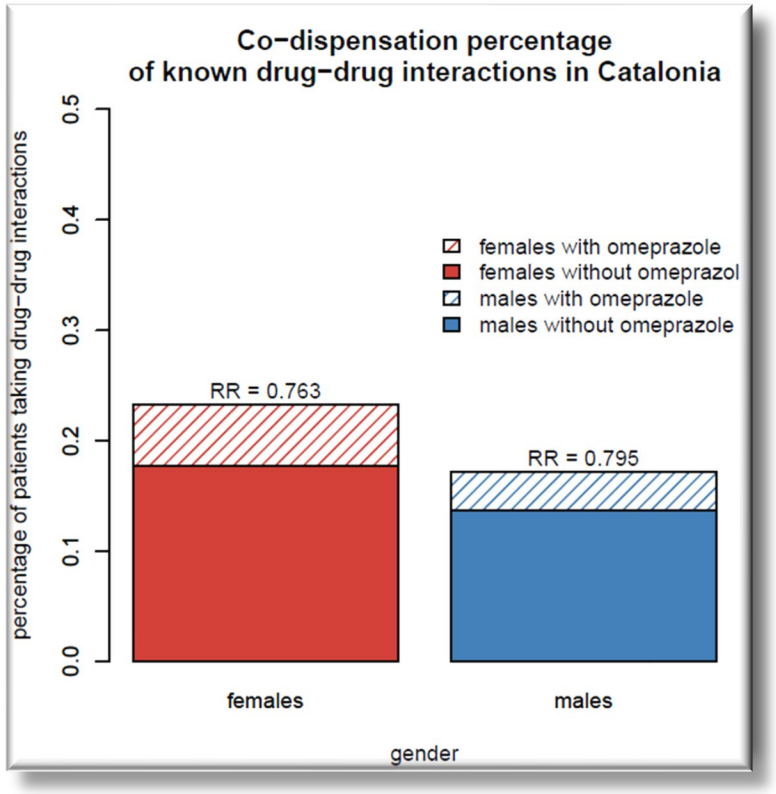

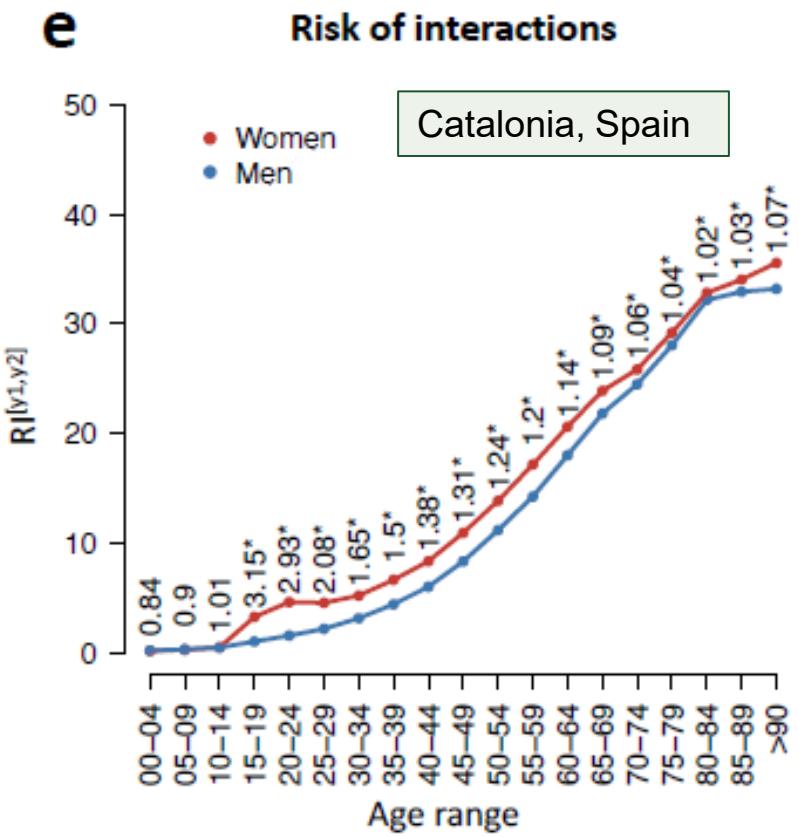

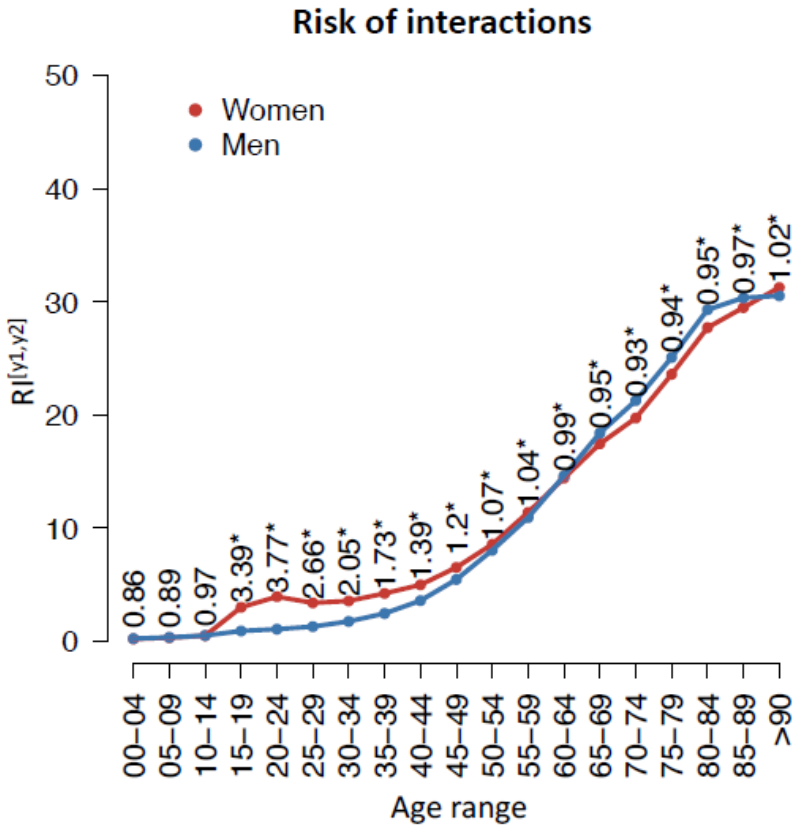

what actionable interventions?

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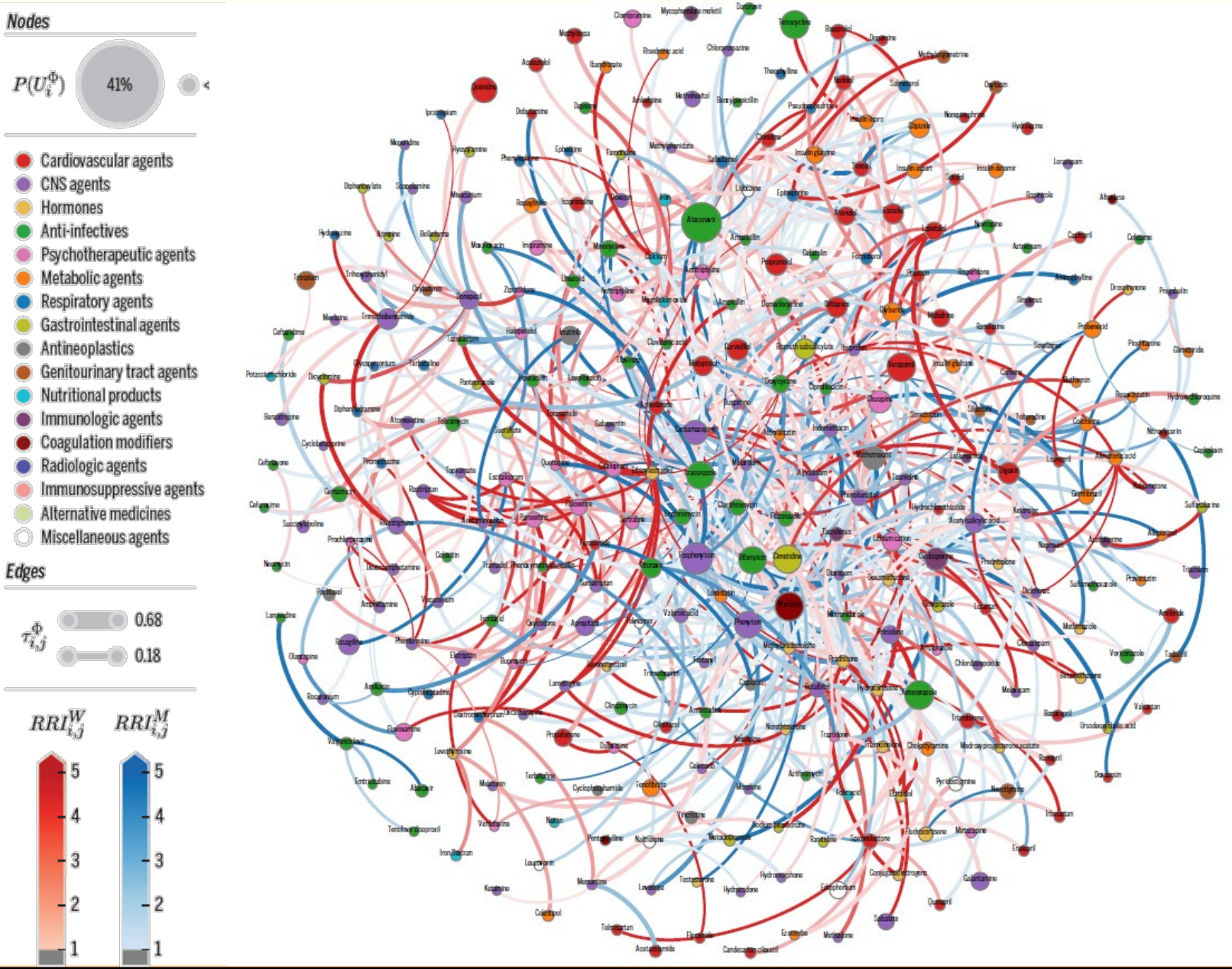
How is the DDI phenomenon in human populations?

Browsable networks to synthesize information and aid actionable interventions



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Strength of interaction ≥ 0.18***:*** likelihood of joint administration, given administration of i or j).

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How is the DDI phenomenon in human populations?

Browsable networks to synthesize information and aid actionable interventions

DDInteract | Networks | Co-dispensation patterns | Documentation | Who we are

Select the population of interest: Catalonia

Select the age range of interest: All

Select the severity of the interactions: All

Select the gender associated risk: All

Select the significant interactions: All

Select the strength of the association:

Co-administration patterns of interacting drugs vary depending on age, gender and healthcare system

Red edges denote a higher risk for females
Blue edges denote a higher risk for males
The edges' width denote the strength of the association of interacting drugs (see Documentation)
The size of the node represents the propensity to be involved in an interaction (see Documentation)
Nodes are colored based on the category they belong to (drugs.com)

Select your drug of interest

disease-perception.bsc.es/ddinteract/

Drug categories:
Nutritional products
Coagulation modifiers
Metabolic agents
Hormones
Miscellaneous agents
Genitourinary tract agents
Anti-infectives
CNS agents
Cardiovascular agents
Immunosuppressive agents
Radiologic agents
Immunologic agents
Alternative medicines
Antineoplastics
Gastrointestinal agents
Respiratory agents
Psychotherapeutic agents

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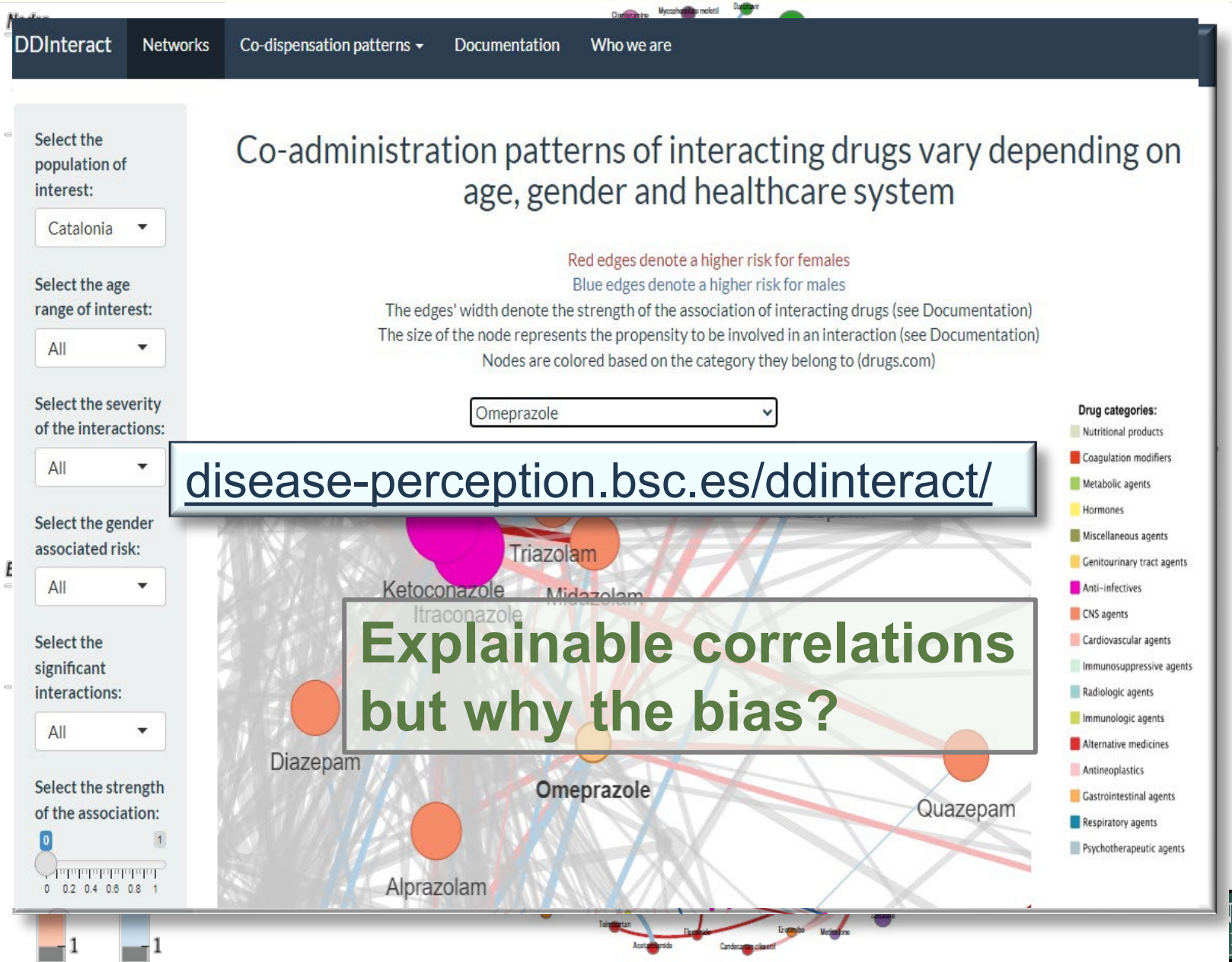

disease-perception.bsc.es/ddinteract/

Explainable correlations but why the bias?

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Indianapolis
1,228 unique *DrugBank* IDs dispensed to **264,607** patients during **2 years** (Jan 2017–Dec 2018).

Blumenau
140 unique *DrugBank* IDs dispensed to **133,047** patients during **18 months** (Jan 2014–Jun 2015).

Strength of interaction ≥ 0.18***:*** likelihood of joint administration, given administration of i or j).

Sanchez-Valle et al [2024].. *BMC Medicine* **22**: 166.

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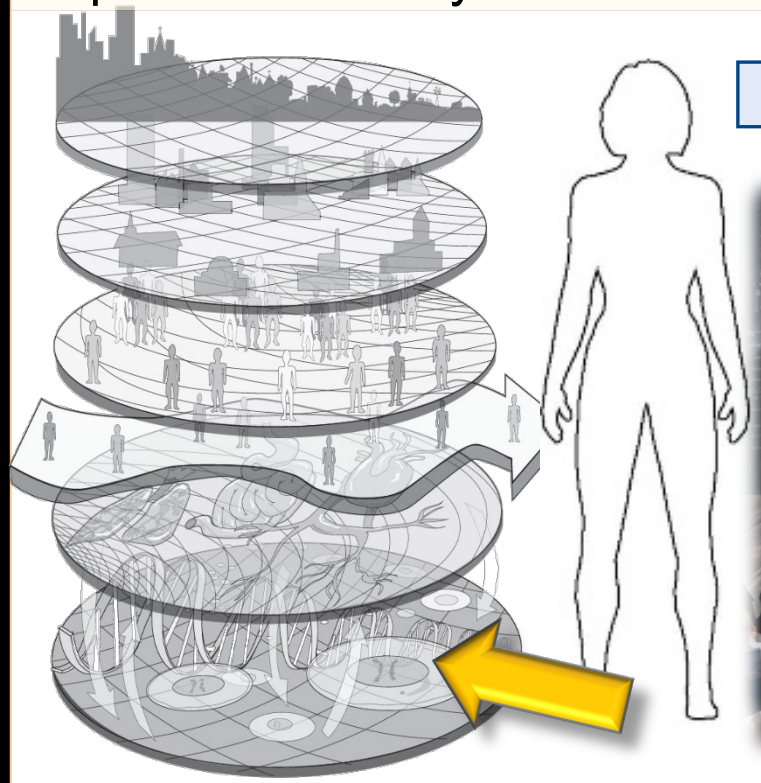
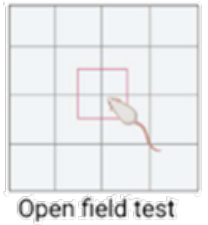
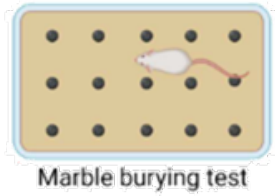
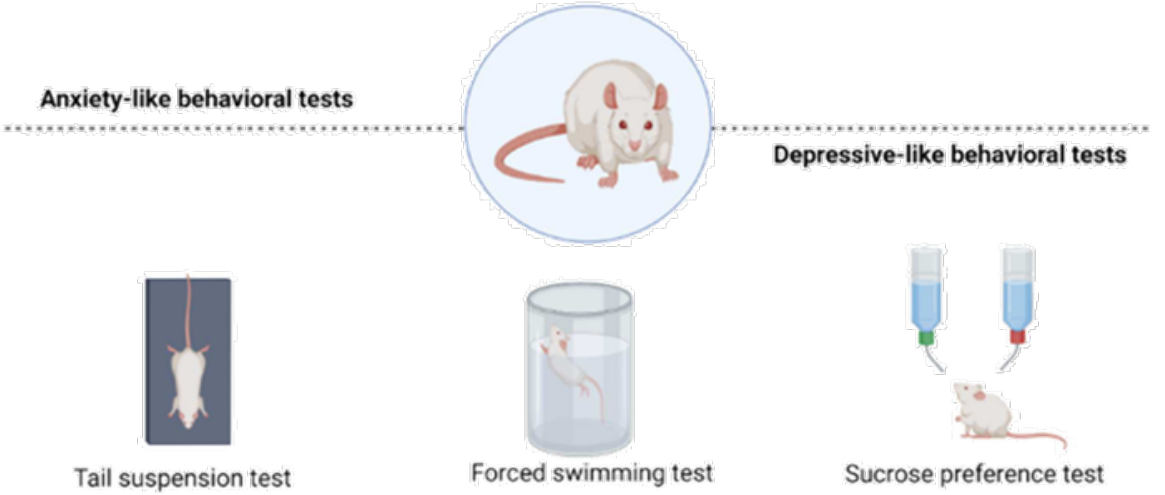
depression/anxiety in mouse models



where is language, society, policy?







- **Mechanistic basis of complex multiscale disease**
  - assumed to reside in the genetic architecture of anxiety and depression
  - at most, in the architecture of the brain.
- **Emphasis on pharmaceuticals as the only interventions derived from "mechanistic understanding."**

Mir, F. R., & Rivarola, M. A. (2022). Sex differences in anxiety and depression: What can (and cannot) preclinical studies tell us? *Sexes*, **3**(1), 141-163.

Pescosolido, B.A. 2006. Journal of Health and Social Behavior 47: 189-208.

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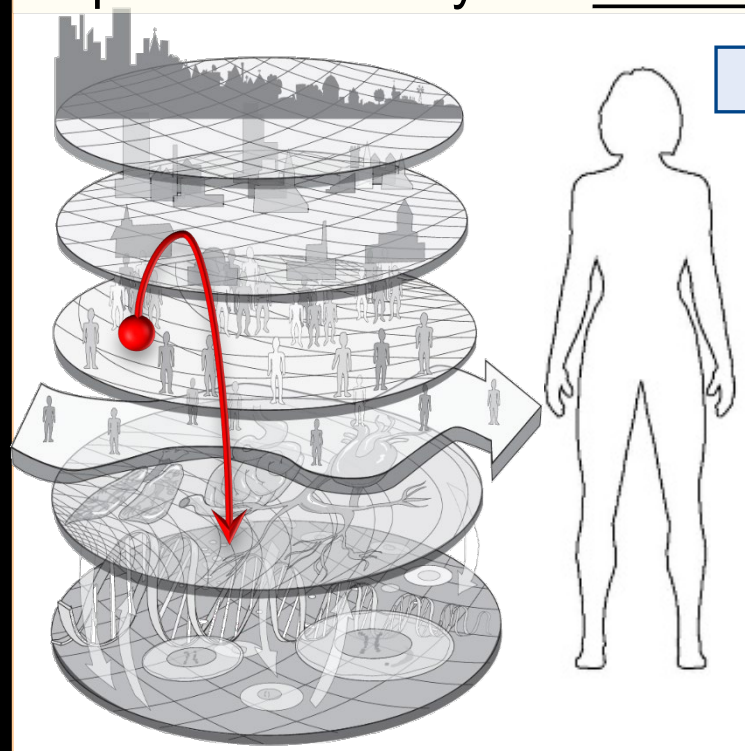
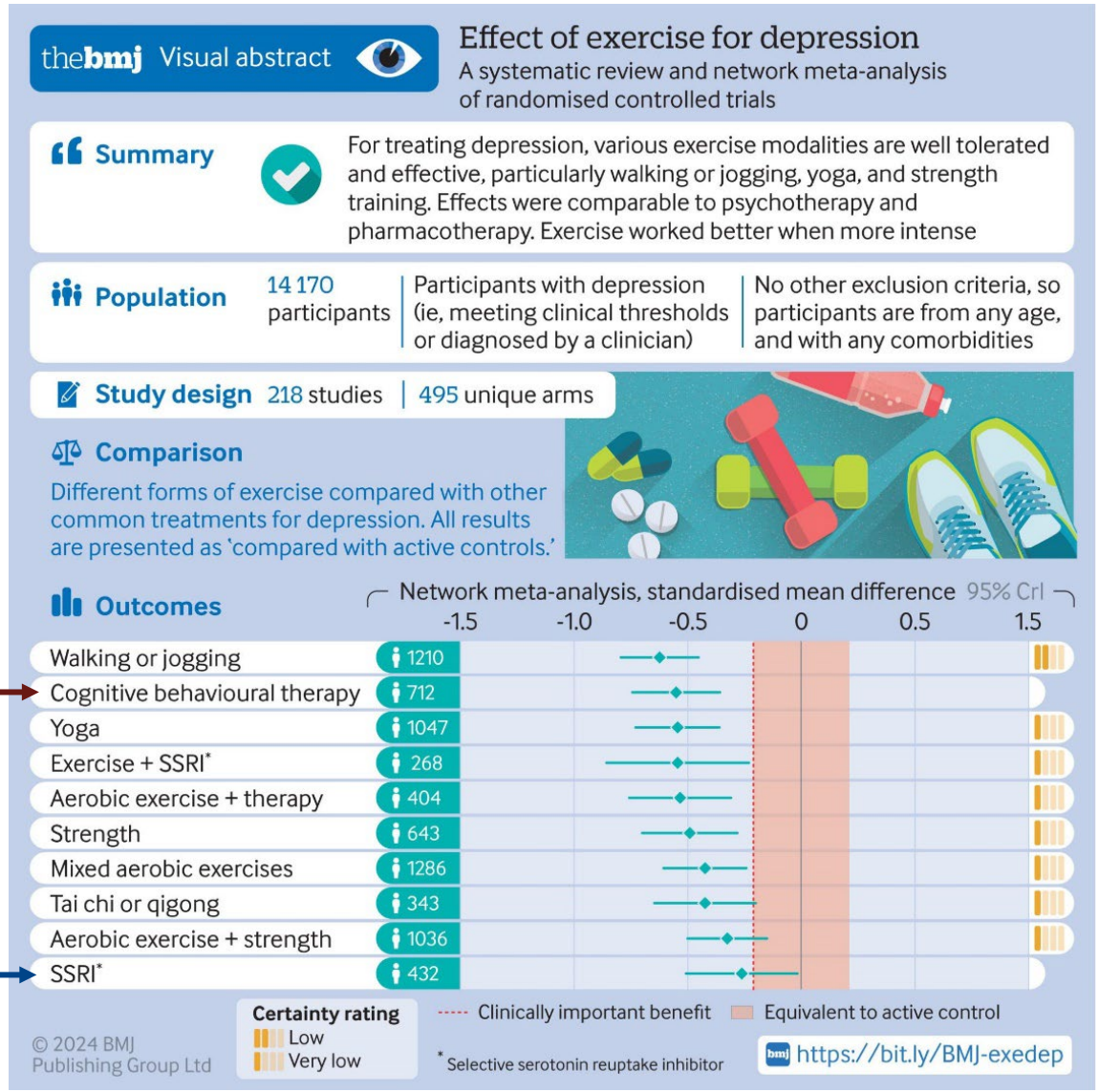
What is the best “mechanism” for intervention in psychopathology

depression/anxiety in a *multiscale* view of human disease



where is language, society, policy?

“**Mechanism**” in complex multiscale disease assumed to reside in **molecular architecture**.
Interventions: pharmaceutical, molecular, cellular…



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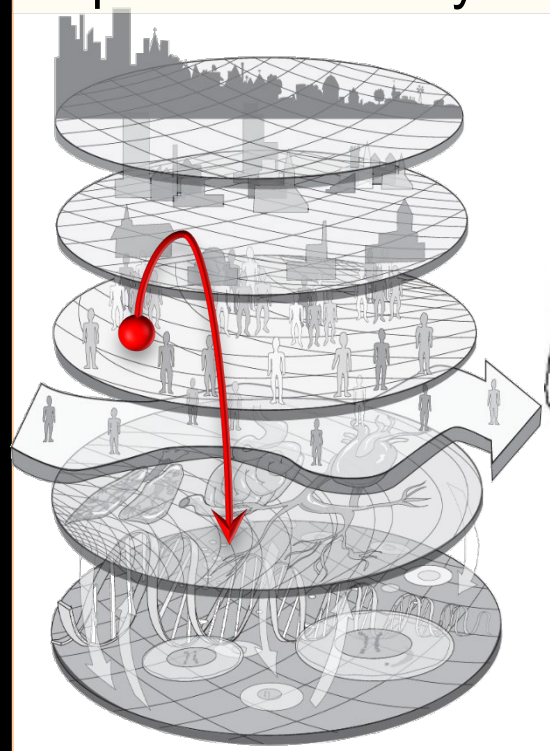

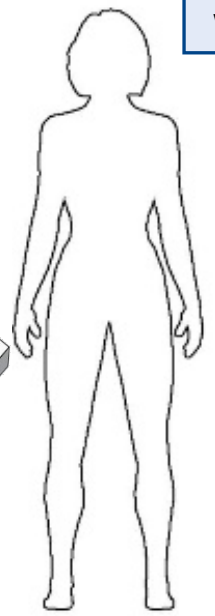

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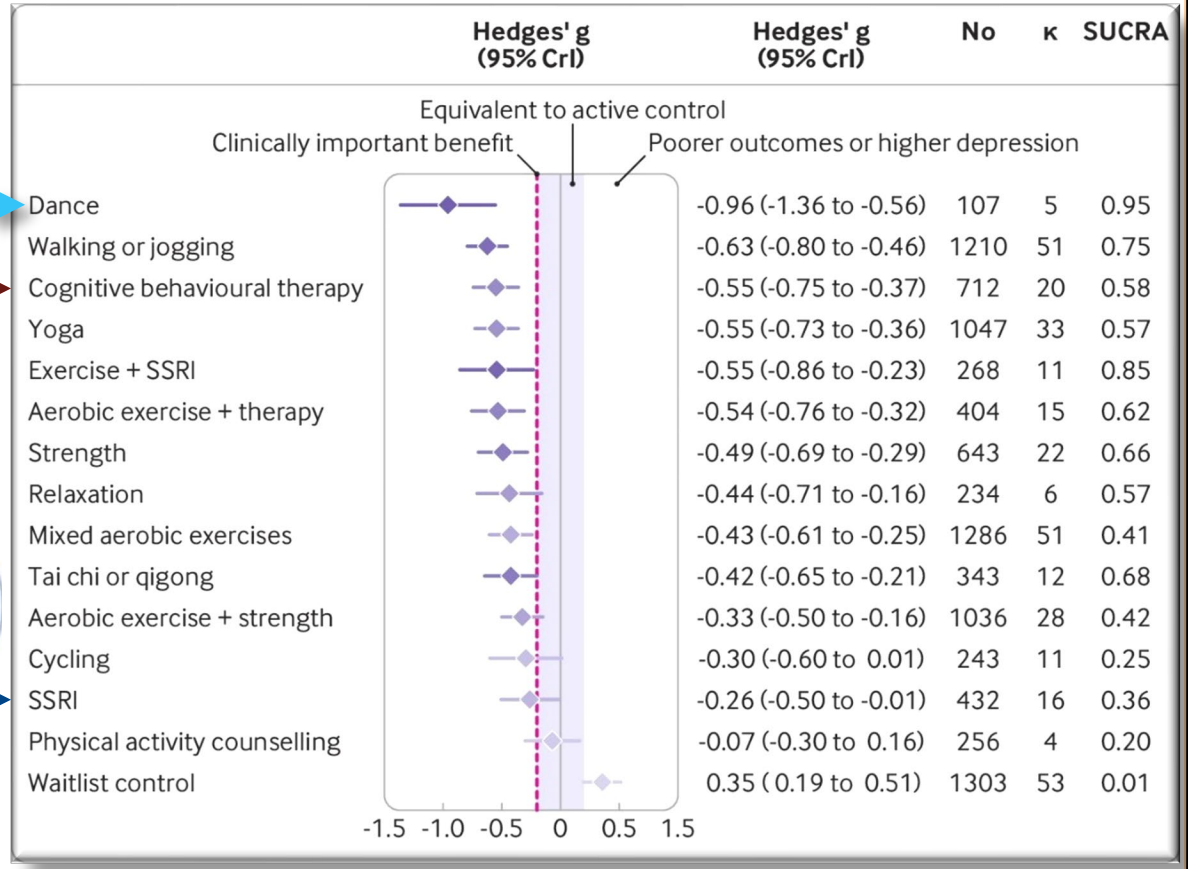

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HEALTH AFFAIRS > VOL. 43, NO. 10: CHILDREN, MEDICARE, PHARMACEUTICALS & MORE

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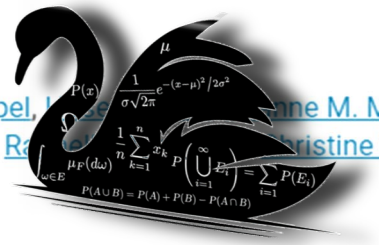
FDA antidepressant warnings of suicide risk among kids may have the opposite effect, study finds

Stephen B. Soumerai, Ross Koppel, [illegible] Madden, Andra Fry, Alyssa Halbisen, Jesenia Angeles, Jonah Koppel, Ra[illegible]ristine Y. Lu

AFFILIATIONS

PUBLISHED: OCTOBER 2024 Open Access https://doi.org/10.1377/hlthaff.2023.00263



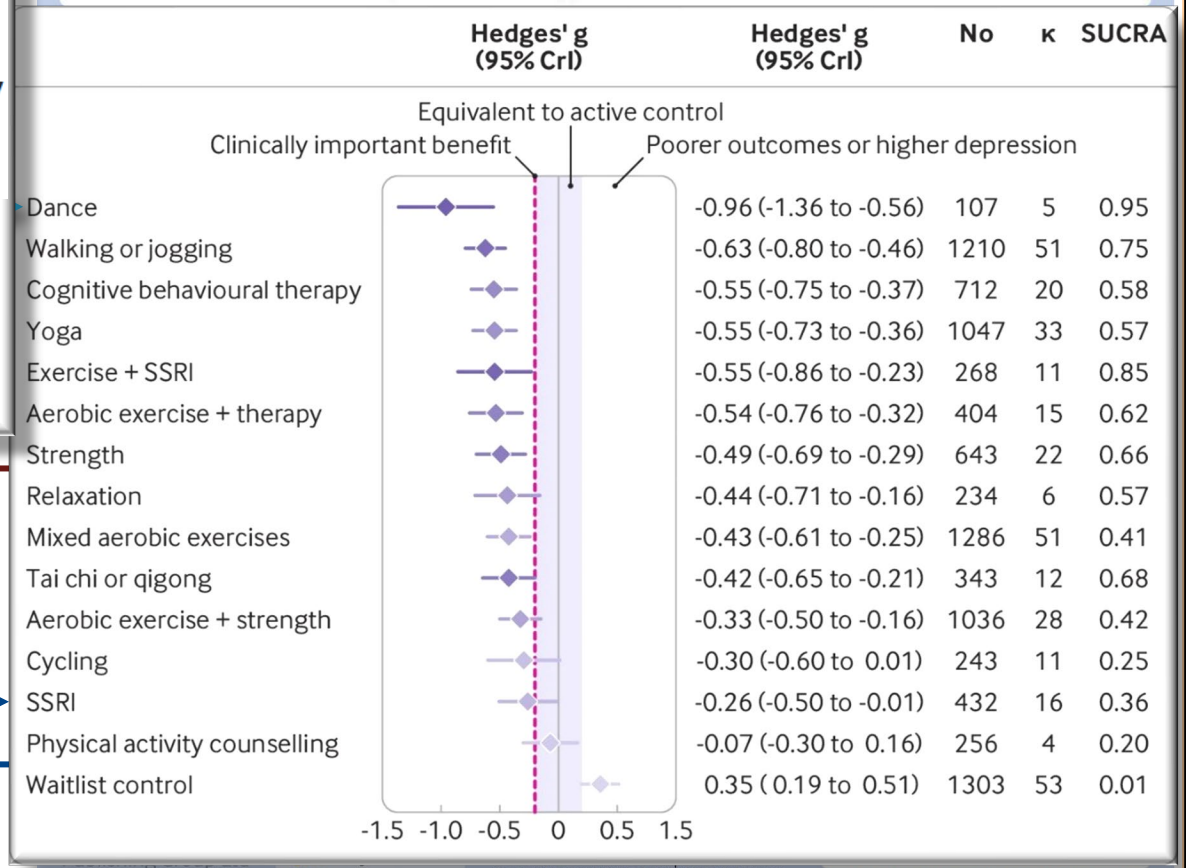
"**Mechanism**" in complex multiscale disease assumed to reside in **molecular architecture**.
Interventions: pharmaceutical, molecular, cellular…

thebmj Visual abstract

Effect of exercise for depression
A systematic review and network meta-analysis of randomised controlled trials

Summary

For treating depression, various exercise modalities are well tolerated and effective, particularly walking or jogging, yoga, and strength training. Effects were comparable to psychotherapy and pharmacotherapy. Exercise worked better when more intense



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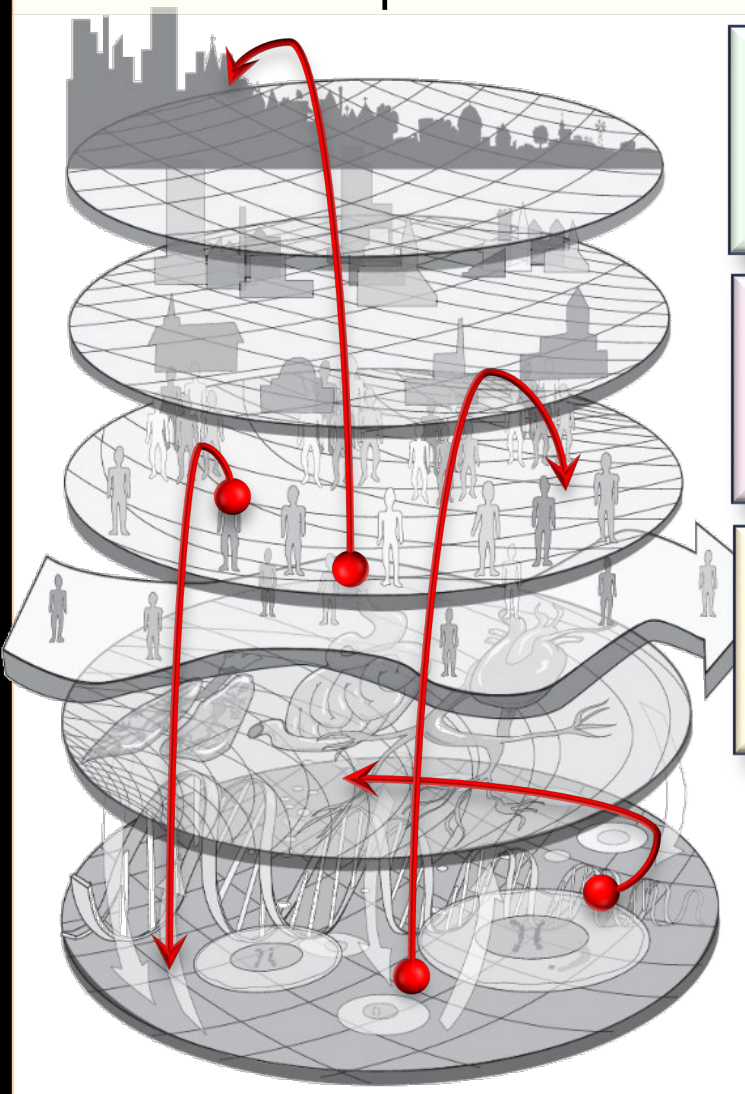
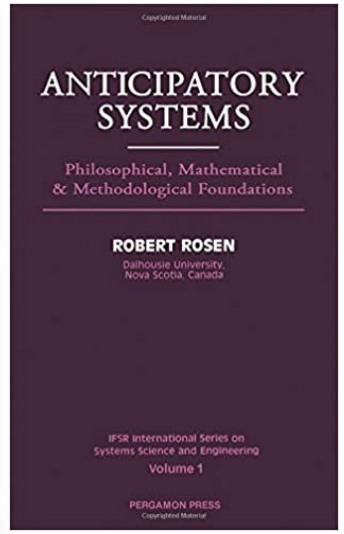
mechanism depends on control hierarchies that are not fully separable (near-decomposable)



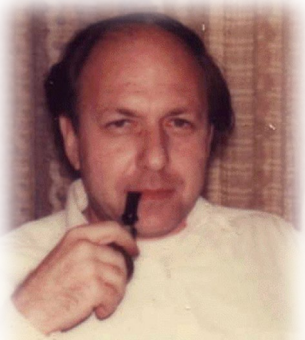
Key insight: complex systems are: 1) not reducible to self-contained multivariate structure or dynamics (boxed mechanisms), 2) not predictable from past data when it matters.

Key insight: complex systems need multi-level, **models and theory** to predict rare, major transitions (not predictable by empirical evidence from single layer)

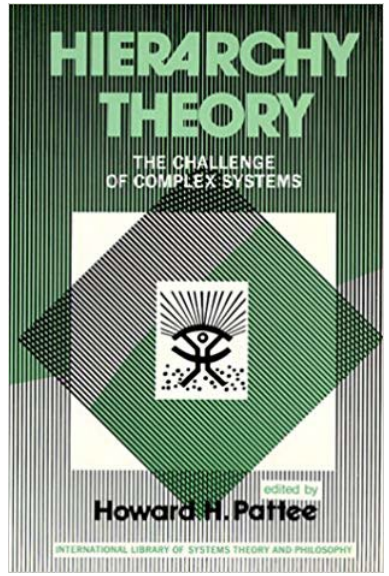
Key insight: best set of levels to understand, predict ,and control complex systems needs to be agnostically and pragmatically estimated from multivariate, multi-level data/evidence



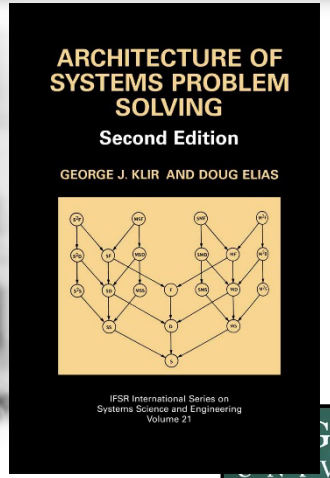
Howard Pattee



Robert Rosen



George Klir



epistemic/pragmatic nature of mechanism?

Pescosolido, B.A. 2006. *Journal of Health and Social Behavior* **47**: 189-208.

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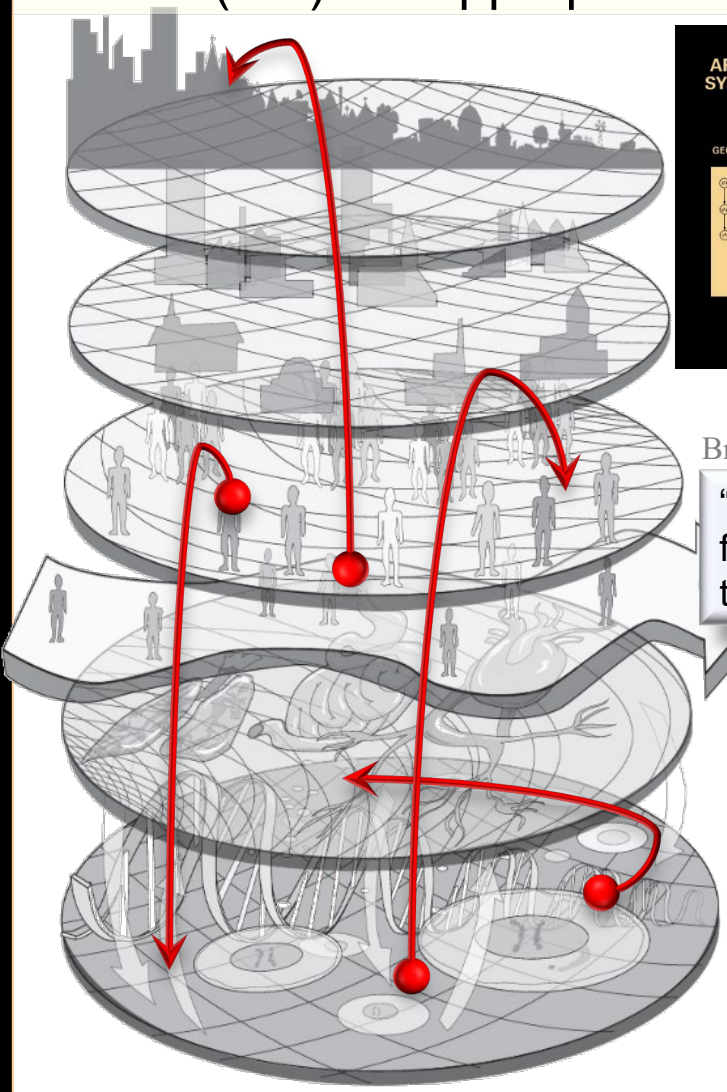
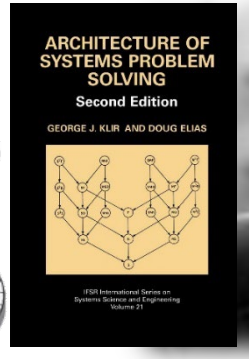
what is (are) the appropriate level(s)?

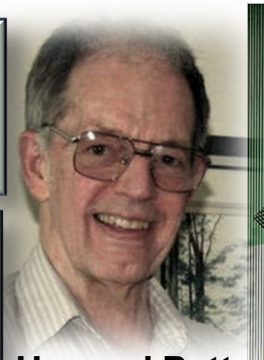


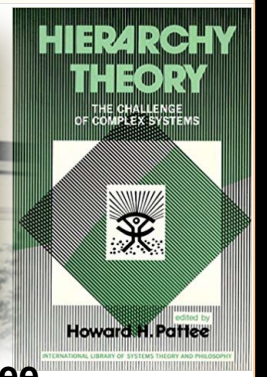



George Klir

Key insight: complex systems not reducible to single level and deviate from past data eventually

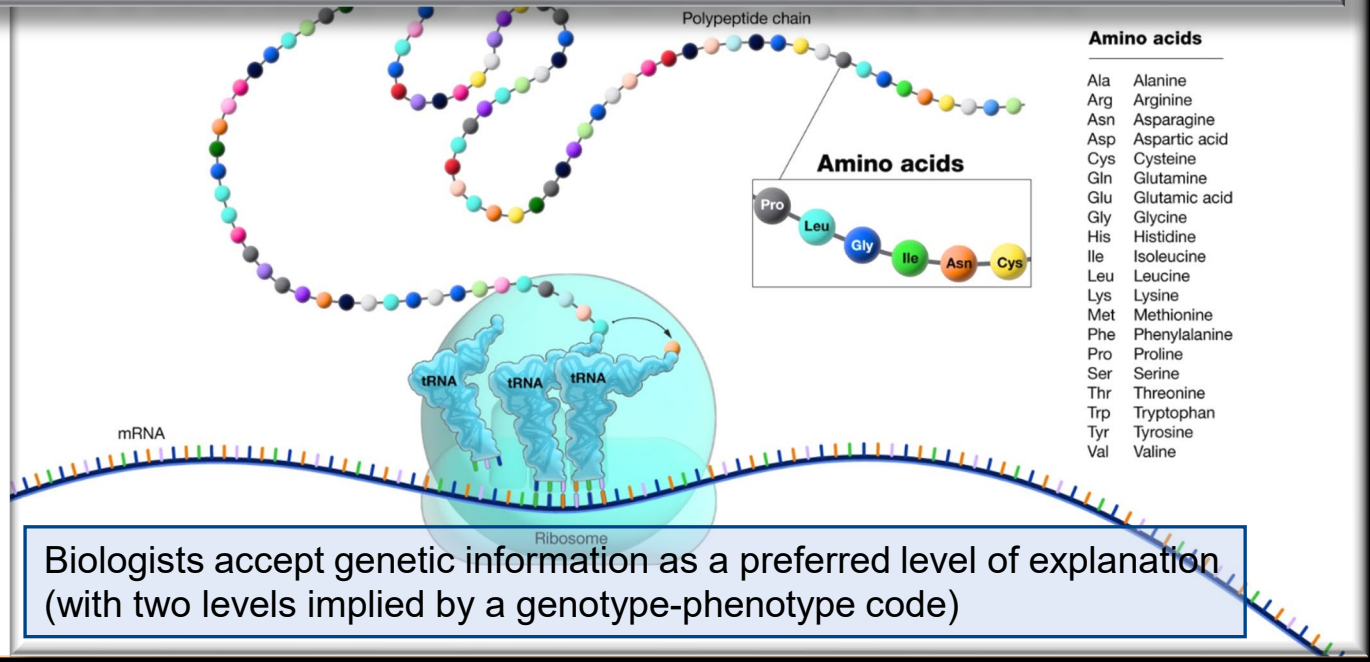
Key insight: appropriate level of description of complex systems must be agnostically and pragmatically estimated


Howard Pattee



Brenner, Sydney. [2012]. "Life's code script." *Nature* **482** (7386): 461-461.

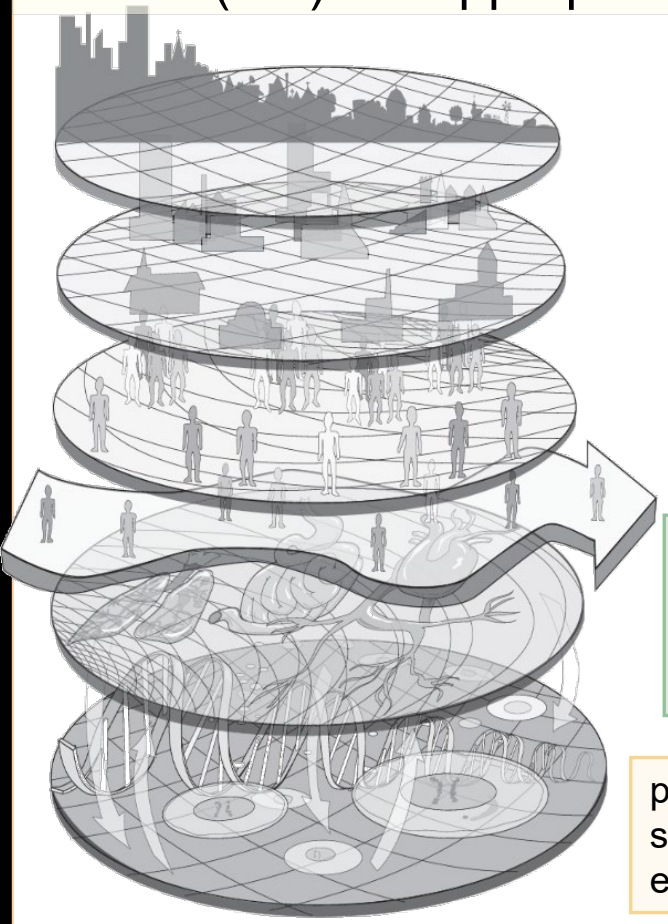
"The concept of the gene as a symbolic representation of the organism — a ***code script*** — is a fundamental feature of the living world and must form the kernel of biological theory. […] at the core of everything are the tapes containing the descriptions to build these special Turing machines." (Sydney Brenner)

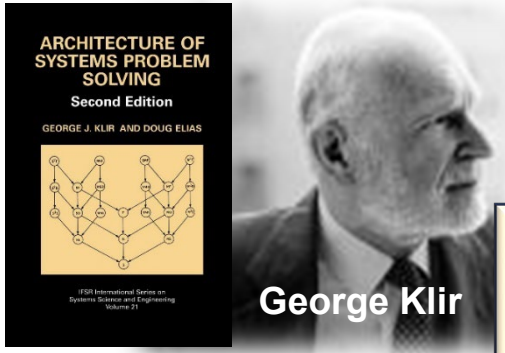


epistemic/pragmatic nature of mechanism?

Biologists accept genetic information as a preferred level of explanation (with two levels implied by a genotype-phenotype code)

what is (are) the appropriate level(s)?





Key insight: complex systems not reducible to single level and deviate from past data eventually

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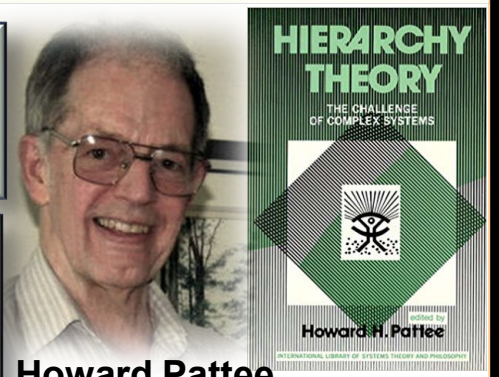
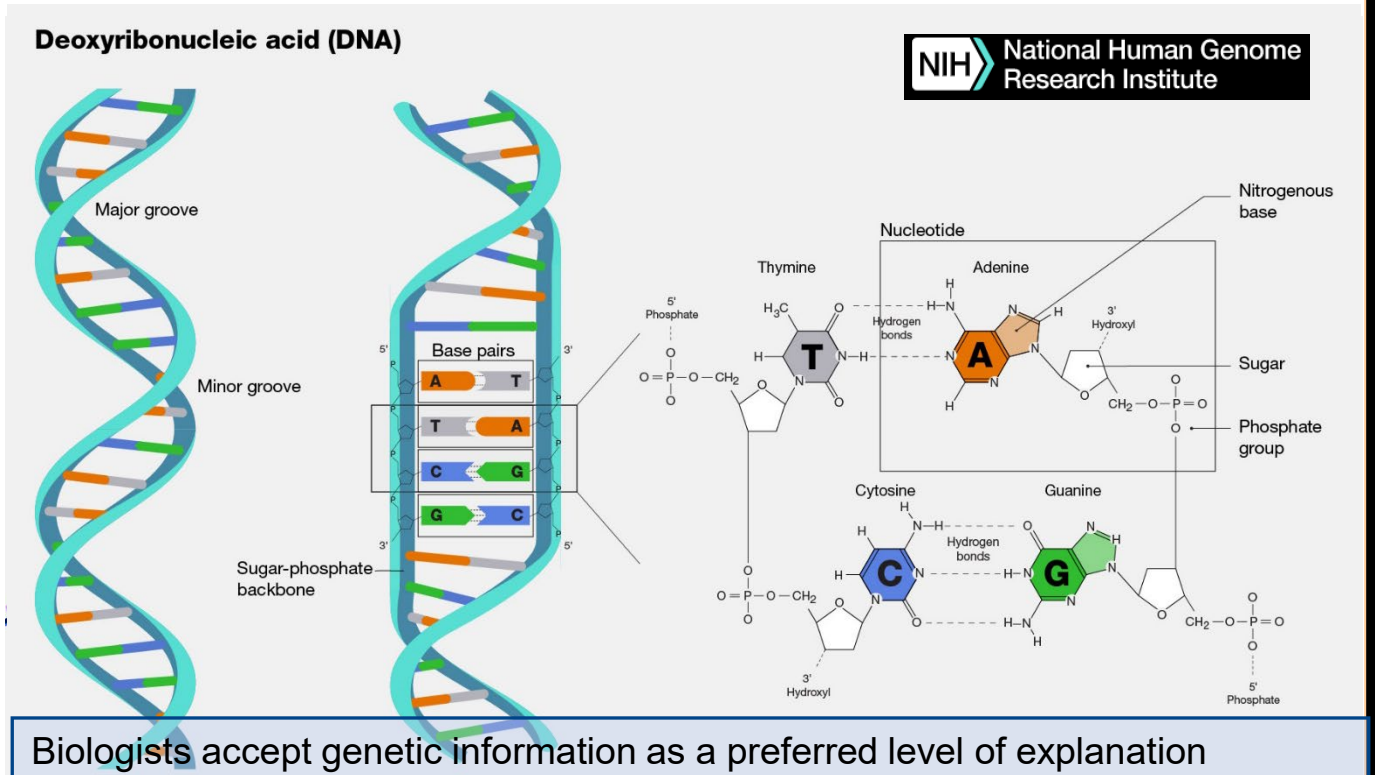


functional (control) hierarchies (especially symbolic codes) establish a “selective loss of detail”.

Not the same as near-decomposability because control hierarchies establish non-holonomic constraints.

preferred levels of explanation should not be assumed, but experimentally established



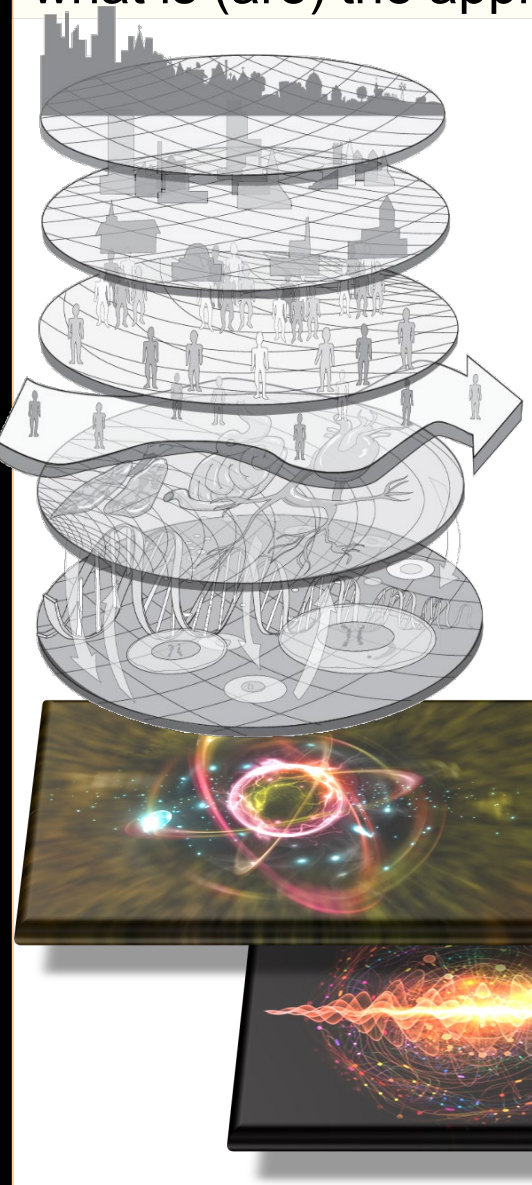
A theory of mechanism is valid if predicted interventions work better than other theories (suggesting ontological nature of theory)

micro-level details below genetic information can be ignored for most functional and evolutionary explanation

epistemic/pragmatic nature of mechanism?

Biologists accept genetic information as a preferred level of explanation

what is (are) the appropriate level(s)?



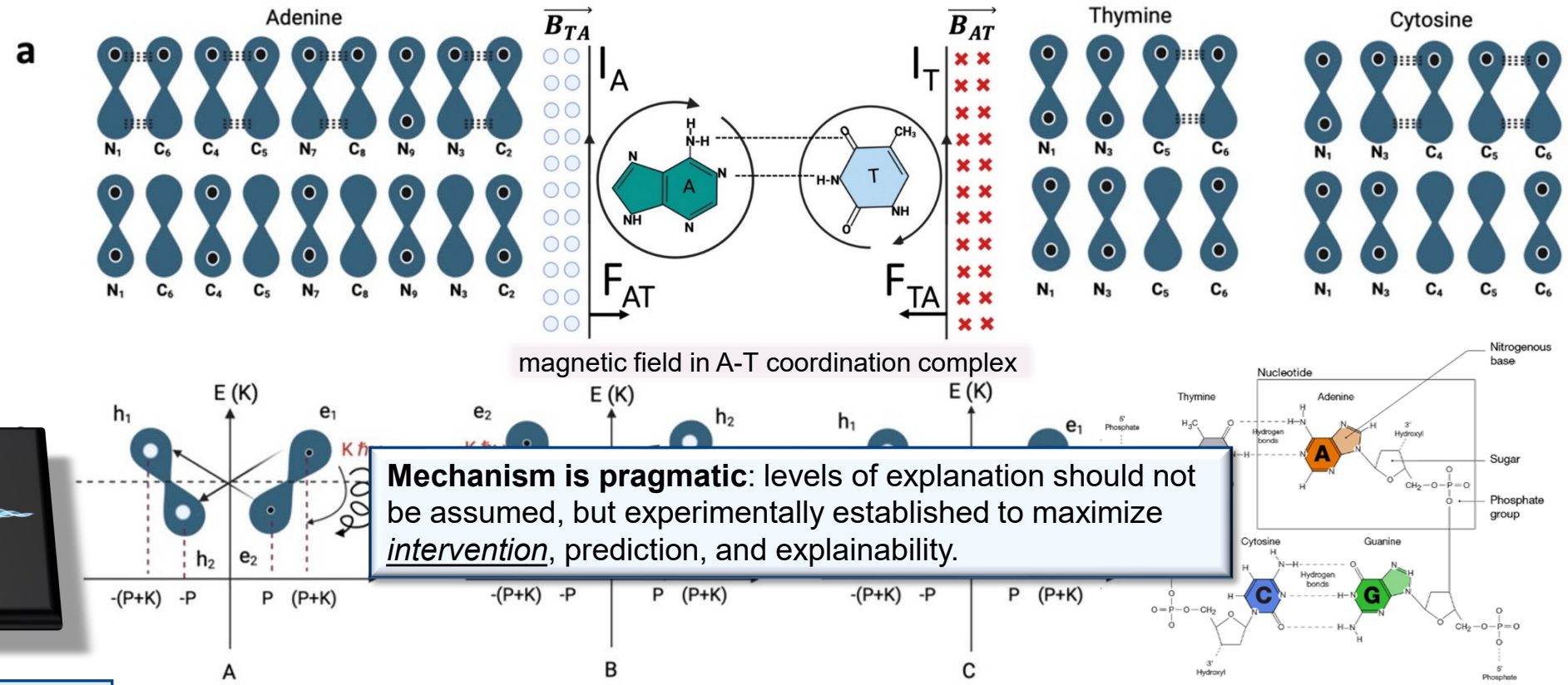
DNA as a perfect quantum computer based on the quantum physics principles

R. Riera Aroche, Y. M. Ortiz García, M. A. Martínez Arellano & A. Riera Leal

Scientific Reports **14**, Article number: 11636 (2024) | Cite this article

micro-level details below genetic information can be ignored for most functional and evolutionary explanation

but lower levels relevant if we are interested, e.g. in DNA as computational memory

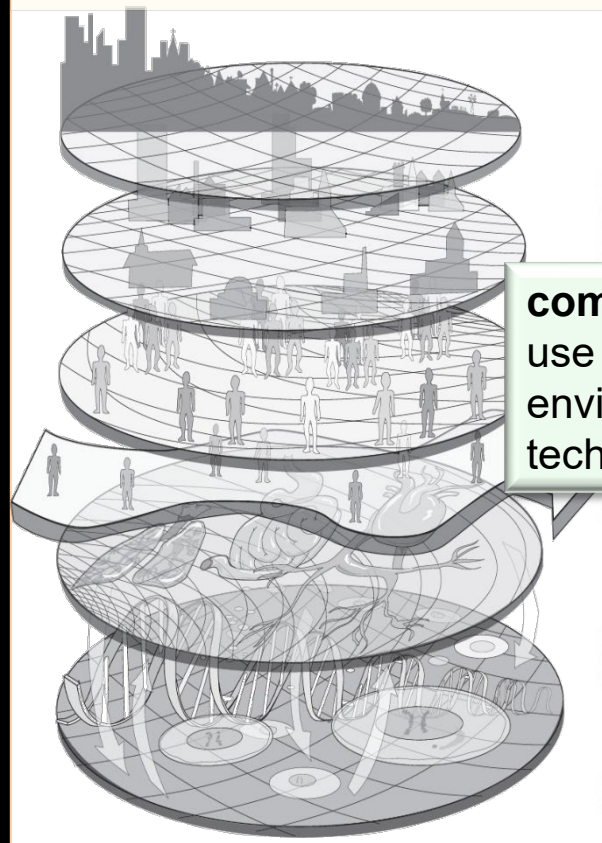


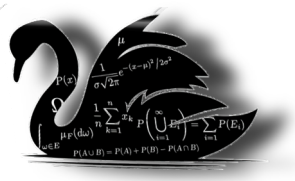
Mechanism is pragmatic: levels of explanation should not be assumed, but experimentally established to maximize *intervention*, prediction, and explainability.

epistemic/pragmatic nature of mechanism?

what is the best “mechanism” for intervention in disease?

multiscale view of disease, including human data

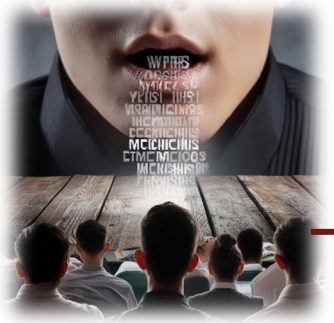




“**Mechanism**” in complex multiscale disease assumed to reside in **molecular architecture**. **Interventions**: pharmaceutical, molecular, cellular…

complex systems, multiscale approach: agnostic use of all *multiomics* levels, as well as medical history, environmental, psychological, linguistic, social, technological, and political layers (*exposome*).

interventions: whatever **mechanism** works best, from pharmaceuticals to policy.



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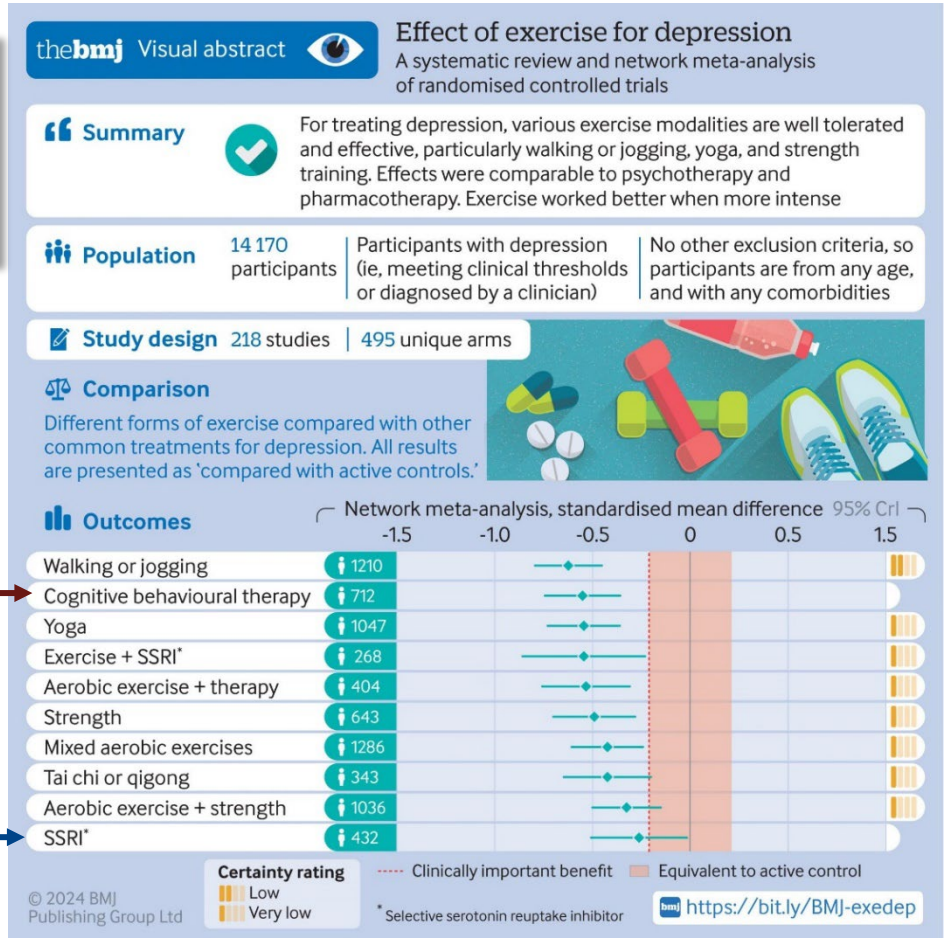

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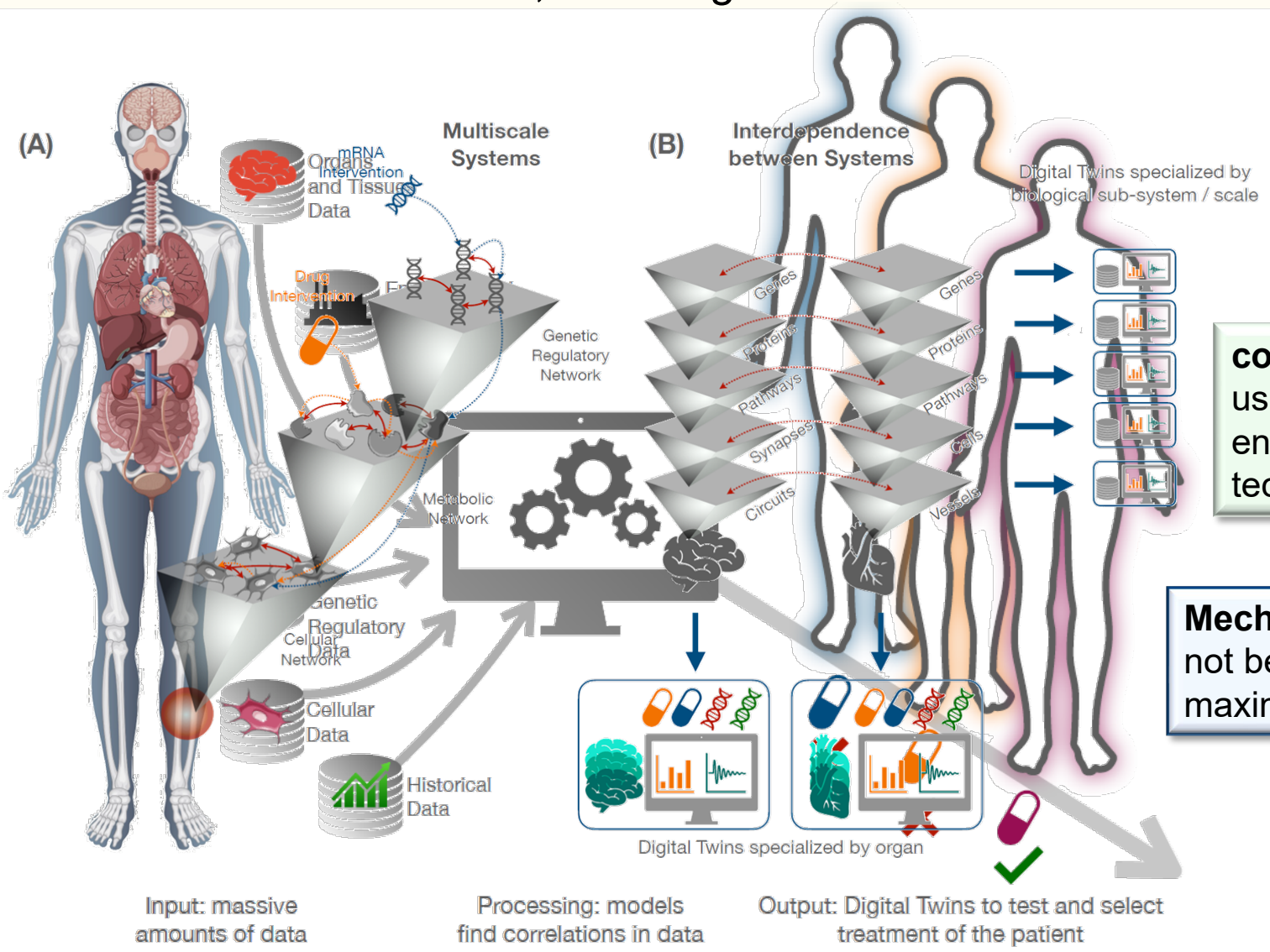
multiscale view of disease, including human data from all levels



Digital twin: in-silico *replication* of a biological cell, sub-system, organ or a whole organism with a transparent predictive model of their relevant ***causal mechanisms*** which responds in the same manner to ***interventions***.

complex systems, multiscale approach: agnostic use of all *multiomics* levels, as well as medical history, environmental, psychological, linguistic, social, technological, and political layers (*exposome*).

Mechanism is pragmatic: levels of explanation should not be assumed, but experimentally established to maximize *intervention*, prediction, and *explainability*

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De Domenico, et al [2025]. "Challenges and opportunities for digital twins in precision medicine: a complex systems perspective". *npj Digital Medicine* **8**, 37.

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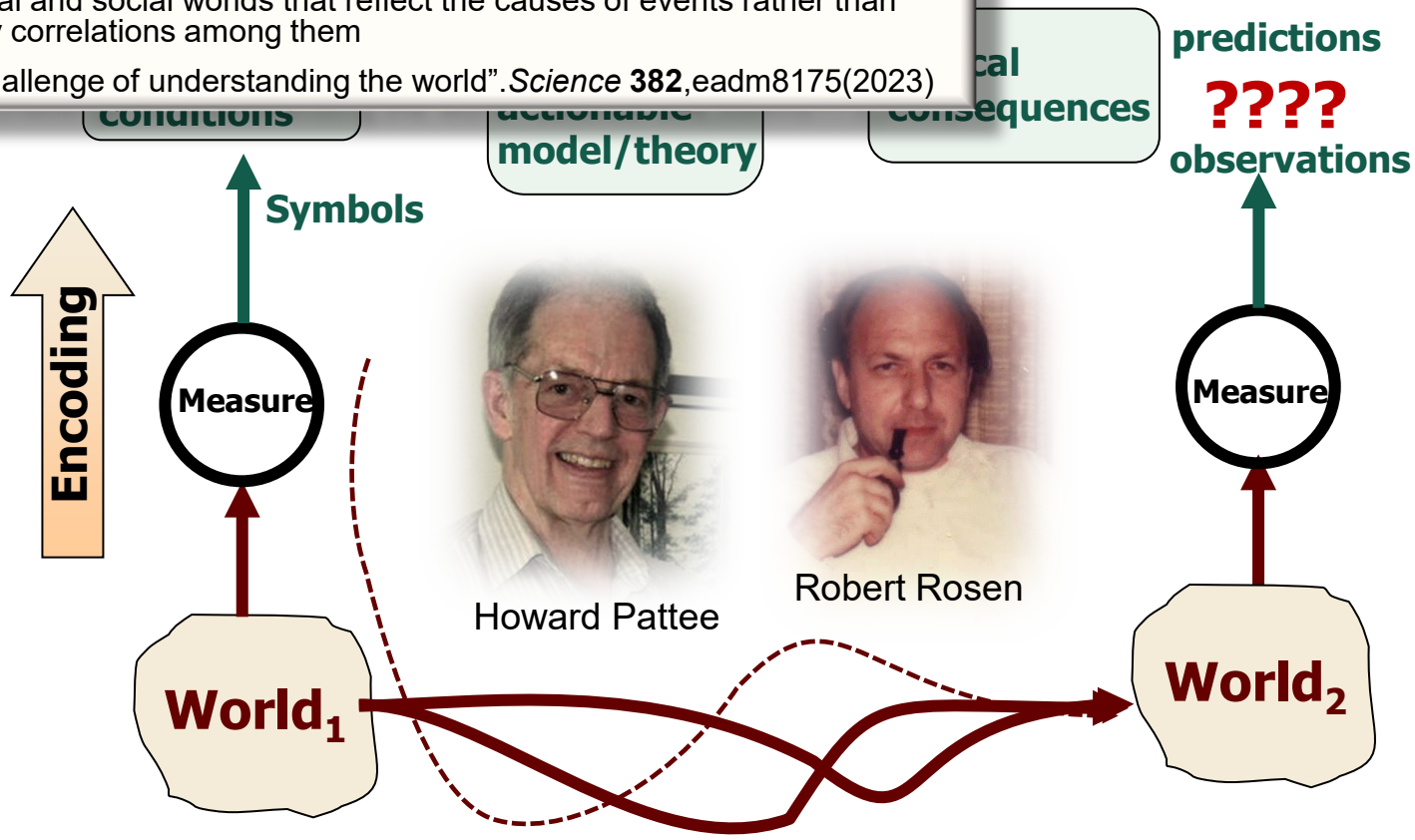
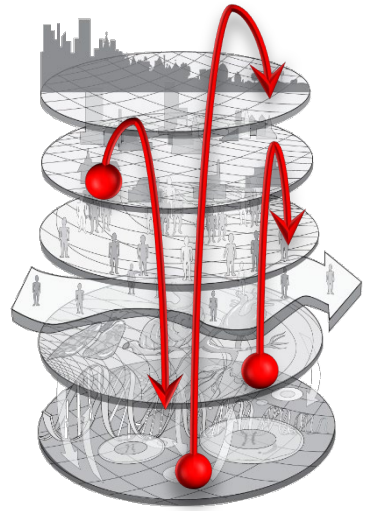
multiscale combination of inductive and deductive actionable models

may work in complex interrelated domain (with rare control events)

Melanie Mitchell: Current AI systems seem to be lacking a crucial aspect of human intelligence: rich internal models of the world. A tenet of modern cognitive science is that humans are not simply conditioned-reflex machines; instead, we have inside our heads *abstracted models* of the physical and social worlds that reflect the causes of events rather than merely correlations among them

AI's challenge of understanding the world". *Science* **382**,eadm8175(2023)





Nassim Nicholas Taleb

"predictions of events **depend** more and more **on theories** when their probability is small and system is **complex**"

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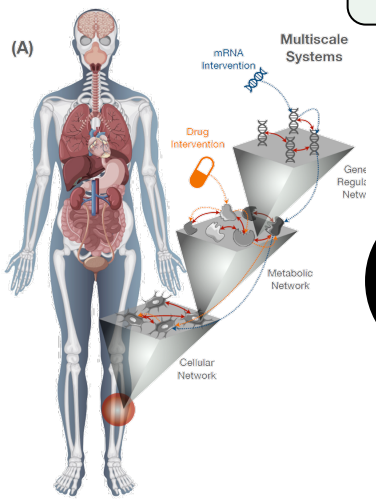
multiscale combination of inductive and deductive actionable models

may work in complex interrelated domain (with rare control events)



unobserved scenarios

examples

Parameter estimation

Initial conditions

Formal, explainable, actionable model/theory

Logical consequences

predictions

????

observations

Particular Instance

General Rule

Symbols

Measure

Measure

Measure

Encoding

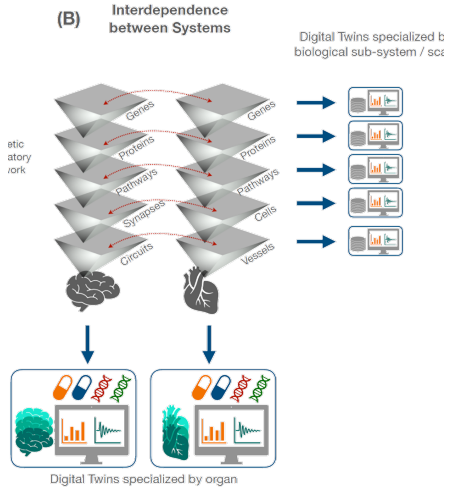
$World_0$

$World_1$

$World_2$

Howard Pattee

Robert Rosen



Nassim Nicholas Taleb

"predictions of events **depend** more and more **on theories** when their probability is small and system is **complex**"

Complex Physical Laws

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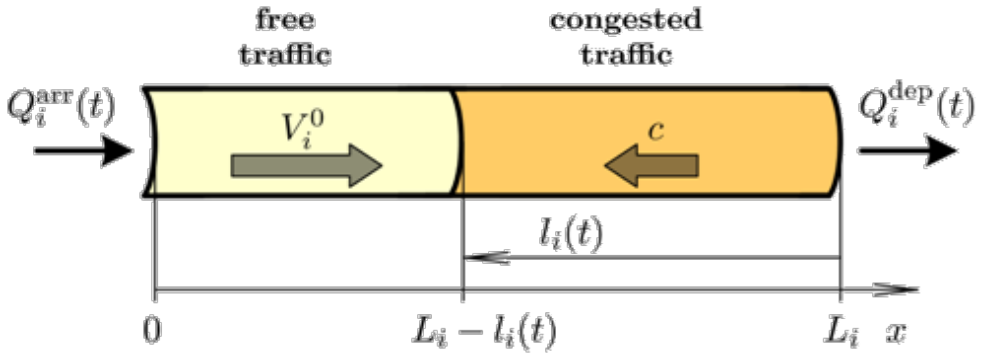
Dirk Helbing's Modeling traffic and human group behavior

- Vehicles and people modeled as particles in a fluid medium
  - Free traffic: behaves as a gas
    - Particles move freely
  - Congested traffic: behaves as a liquid
    - movement of particles strongly depends on surrounding dynamics
  - Shock waves
    - emerge from density variations
    - Example in congested traffic
      - The velocity change of a vehicle propagates (with a homogenous time delay) in the opposite direction of traffic as downstream vehicle respond to changes in upstream vehicles
      - propagation speed aprox. -15 km/h (In free traffic = free vehicle velocity).



D. Helbing: Traffic and related self-driven many-particle systems. *Reviews of Modern Physics* **73**, 1067-1141 (2003).

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- Vehicles and people modeled as particles in a fluid medium
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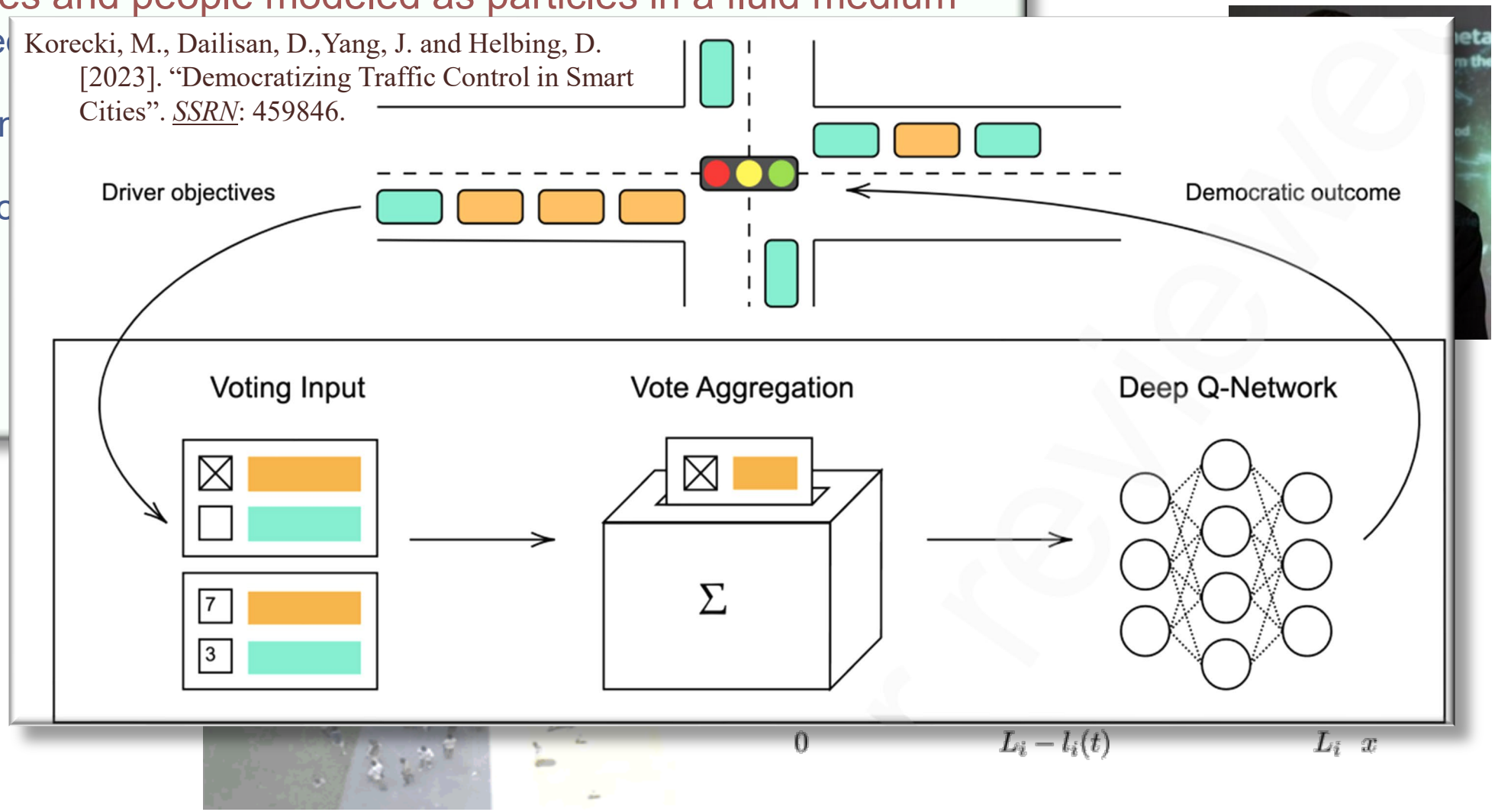
Korecki, M., Dailisan, D.,Yang, J. and Helbing, D. [2023]. "Democratizing Traffic Control in Smart Cities". *SSRN*: 459846.



D. Helbing: Traffic and related self-driven many-particle systems. *Reviews of Modern Physics* **73**, 1067-1141 (2003).

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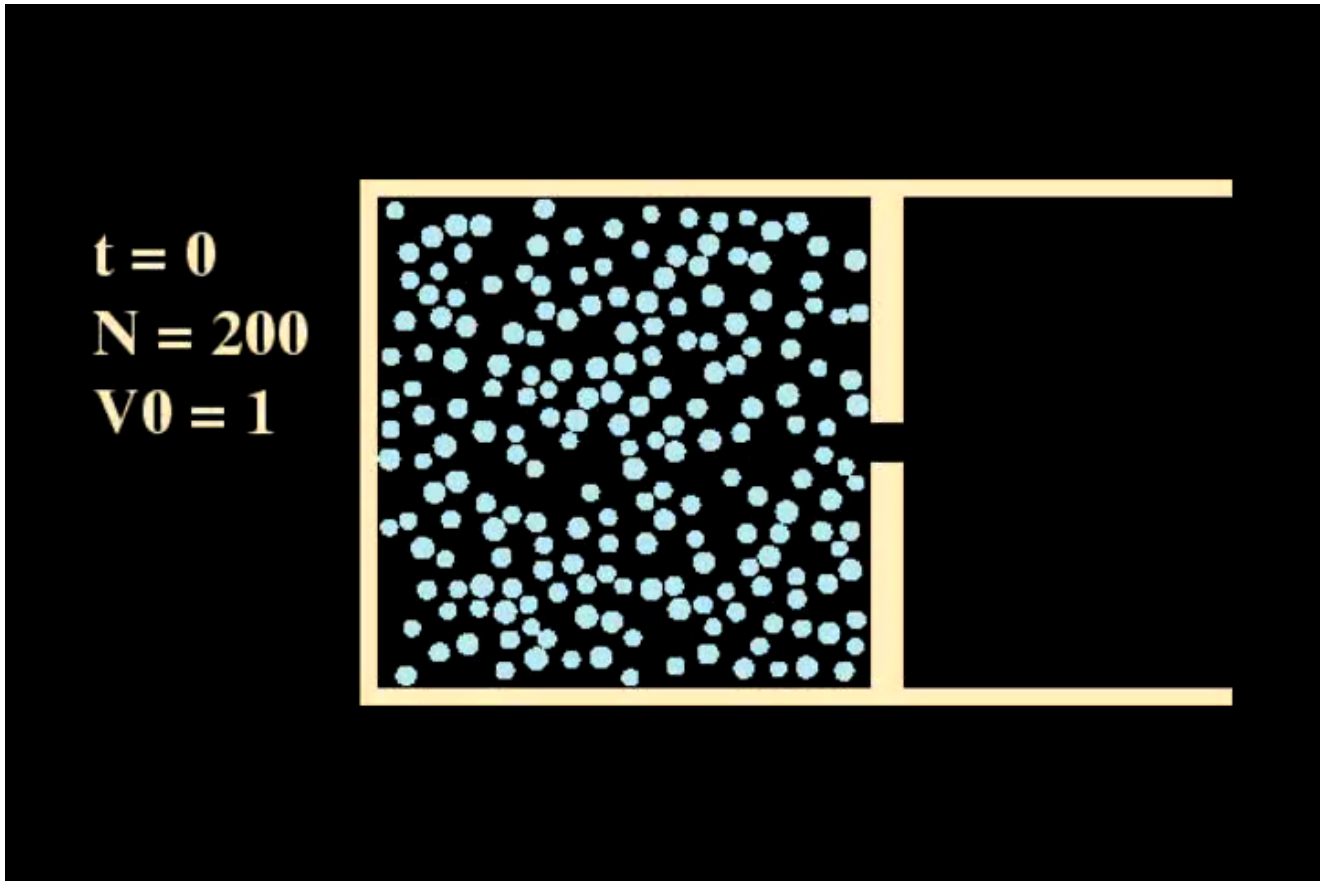
modeling crowd disasters

- People modeled as self-driven many-particle systems
- Testing individualistic vs herding behavior as well as environmental solutions



D. Helbing, A. Johansson and H. Z. Al-Abideen (2007) The Dynamics of Crowd Disasters: An Empirical Study. *Physical Review E* 75, 046109.

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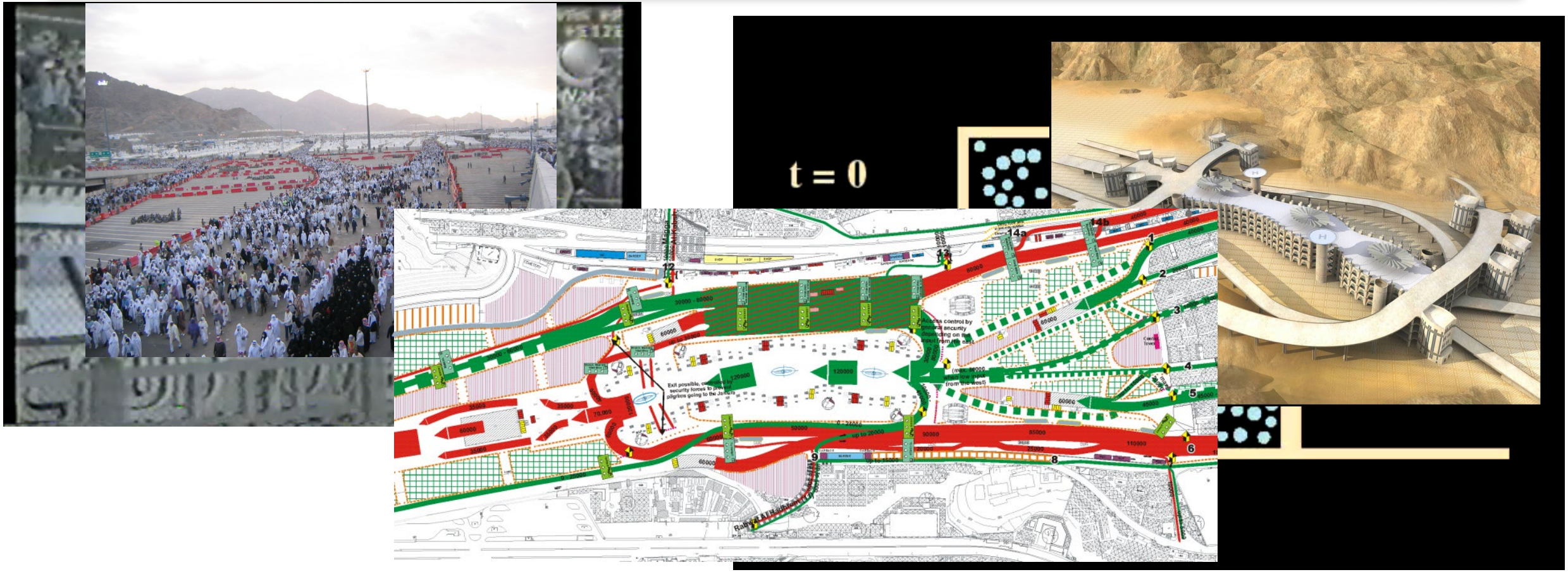

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mechanistic models, estimated parameters

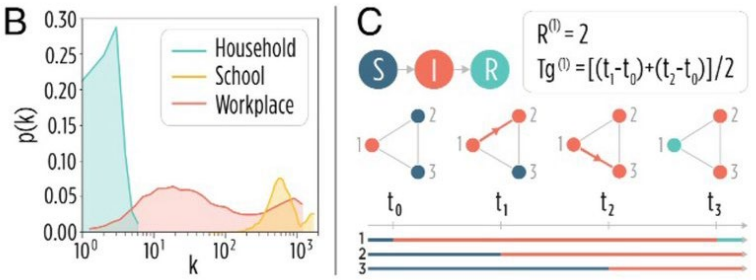
PNAS

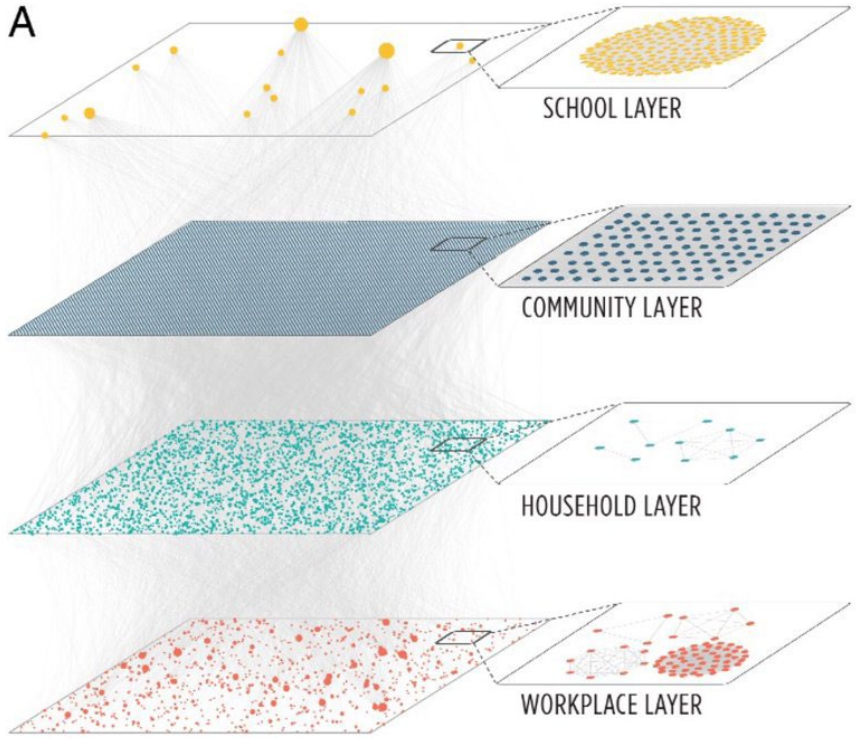
Measurability of the epidemic reproduction number in data-driven contact networks

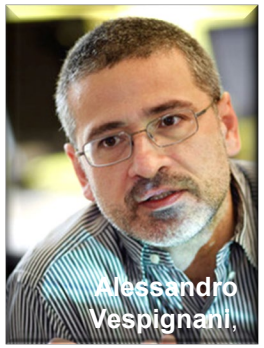
Quan-Hui Liu[a,b,c], Marco Ajelli[c,d], Alberto Aleta[e,f], Stefano Merler[d], Yamir Moreno[e,f,g], and Alessandro Vespignani[c,g,1]

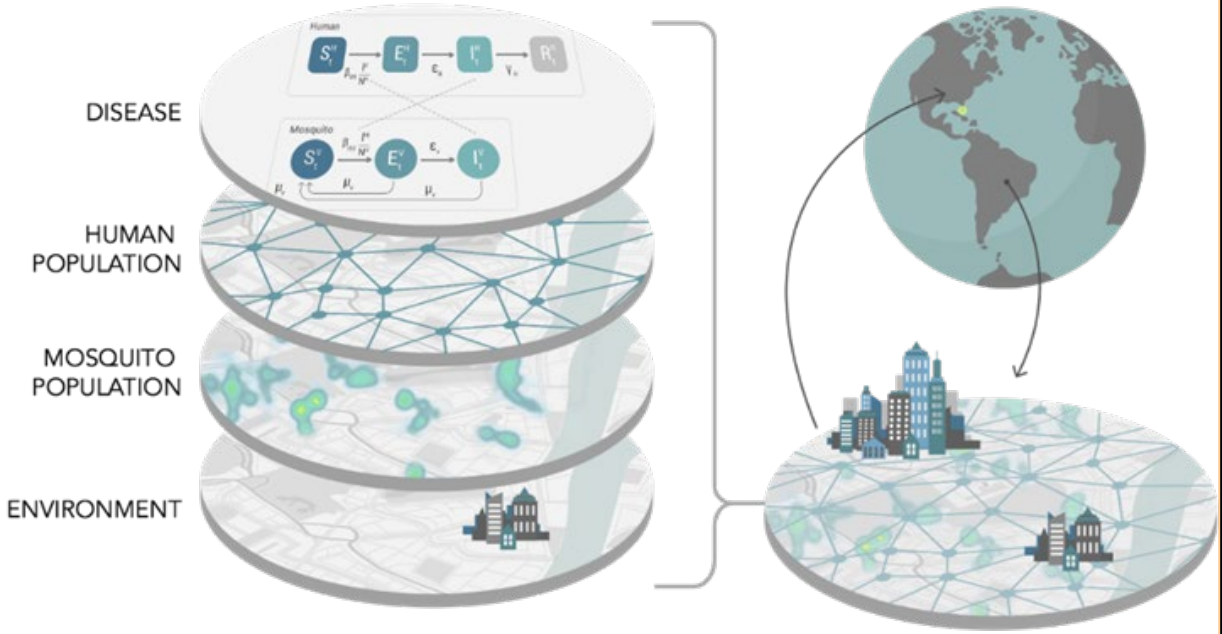
[a]Web Sciences Center, University of Electronic Science and Technology of China, Chengdu 611731, Sichuan, People's Republic of China; [b]Big Data Research Center, University of Electronic Science and Technology of China, Chengdu 611731, Sichuan, People's Republic of China; [c]Laboratory for the Modeling of Biological and Socio-Technical Systems, Northeastern University, Boston, MA 02115; [d]Bruno Kessler Foundation, 38123 Trento, Italy; [e]Institute for Biocomputation and Physics of Complex Systems, University of Zaragoza, 50018 Zaragoza, Spain; [f]Department of Theoretical Physics, University of Zaragoza, 50009 Zaragoza, Spain; and [g]ISI Foundation, 10126 Turin, Italy

Edited by Simon A. Levin, Princeton University, Princeton, NJ, and approved October 16, 2018 (received for review June 27, 2018)









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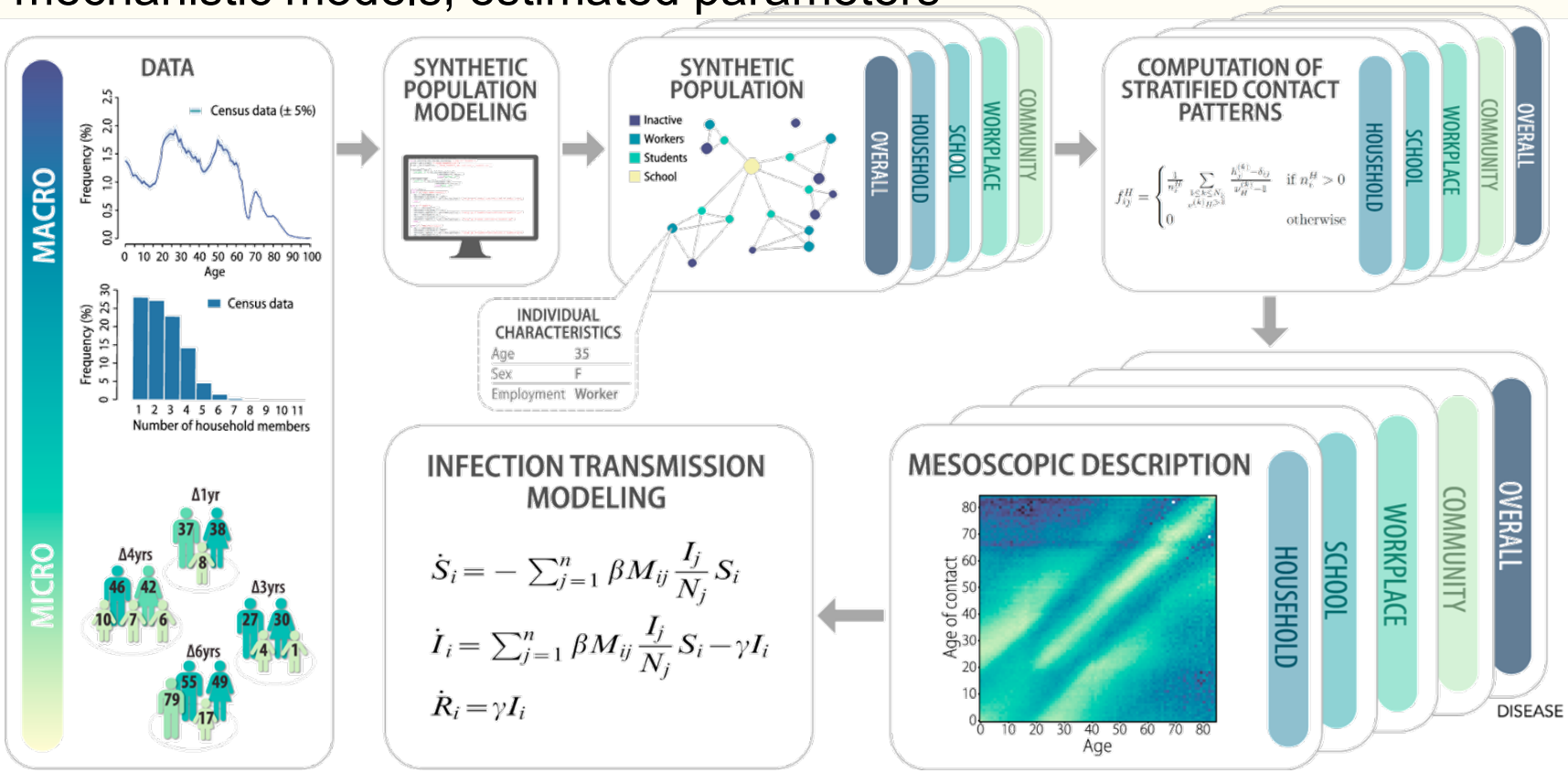

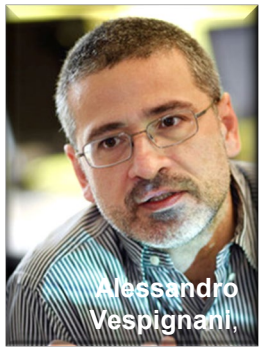

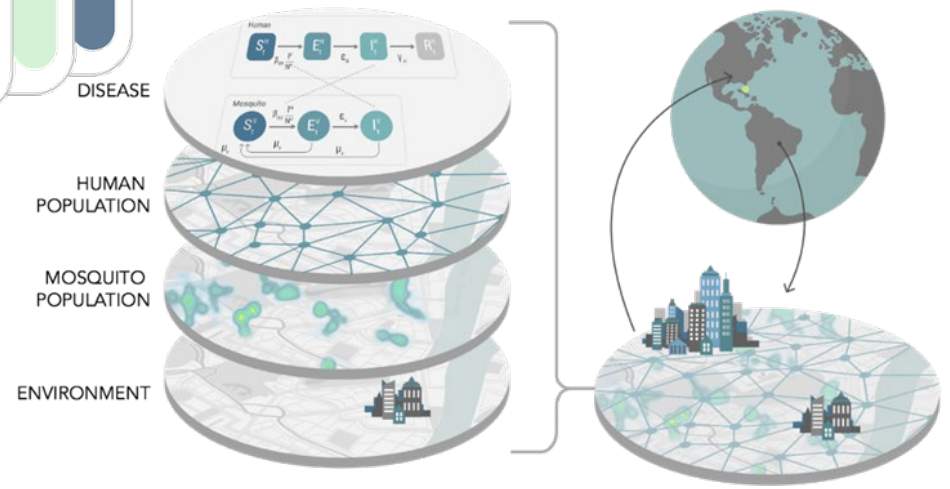

nature COMMUNICATIONS

Inferring high-resolution human mixing patterns for disease modeling

Dina Mistry[1,2], Maria Litvinova[2,3,4], Ana Pastore y Piontti[2], Matteo Chinazzi[2], Laura Fumanelli[5], Marcelo F. C. Gomes[6], Syed A. Haque[2], Quan-Hui Liu[7], Kunpeng Mu[2], Xinyue Xiong[2], M. Elizabeth Halloran[8,9], Ira M. Longini Jr.[10], Stefano Merler[5], Marco Ajelli[2,4]✉ & Alessandro Vespignani[2,3]✉

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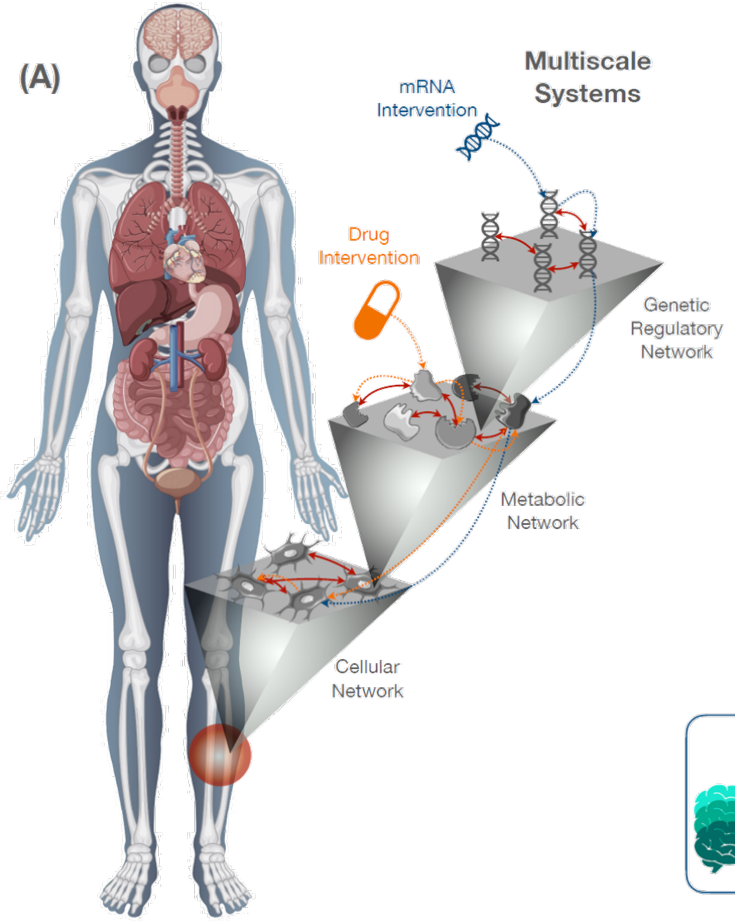
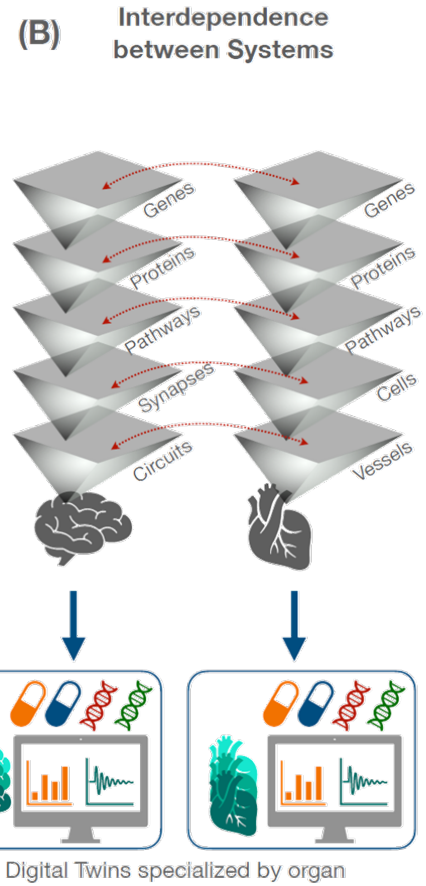
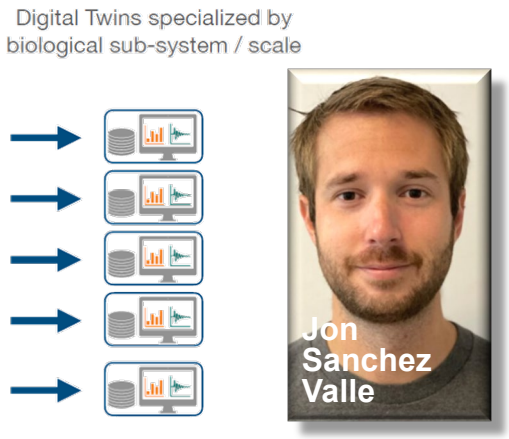
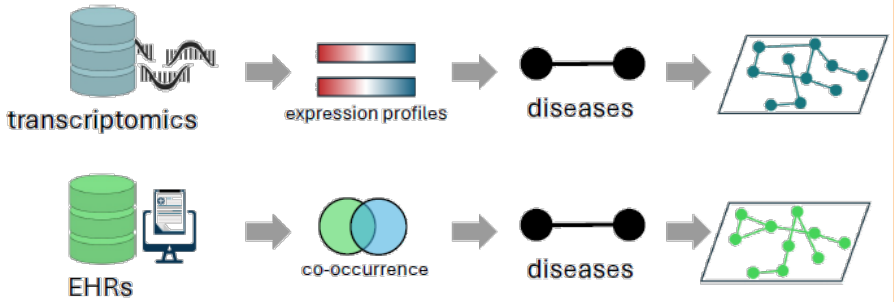
integrating and analyzing multiomics data







Layer	Source
Transcriptomics	GEO
EHRs	Danish population
genes	DisGeNET
miRNAs	HMDD
drugs	CTD
symptoms	HSDN
metabolome	HMDB
microbiome	DISBIOME



complex systems, multiscale approach: agnostic use of all *multiomics* levels, as well as medical history, environmental, psychological, linguistic, social, technological, and political layers (*exposome*).

Sanchez-Valle et al [2020]. *Nature communications*, **11**: 2854.
Núñez-Carpintero et al [2024]. *Nature communications*, **15**:1227.
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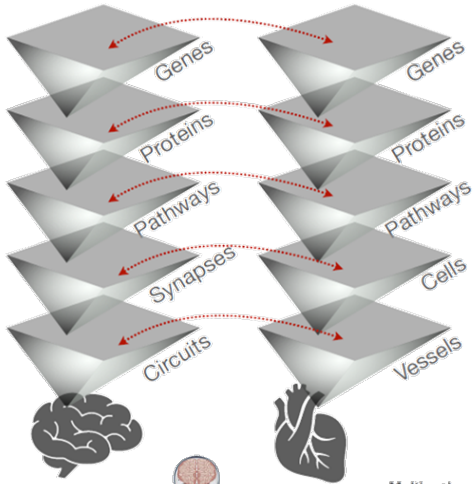
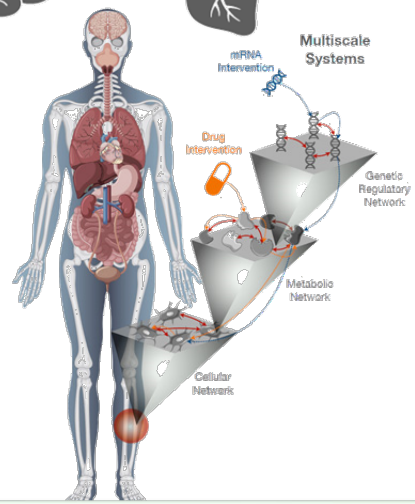
multilayer network models of multiscale interdependence for comorbidity analysis





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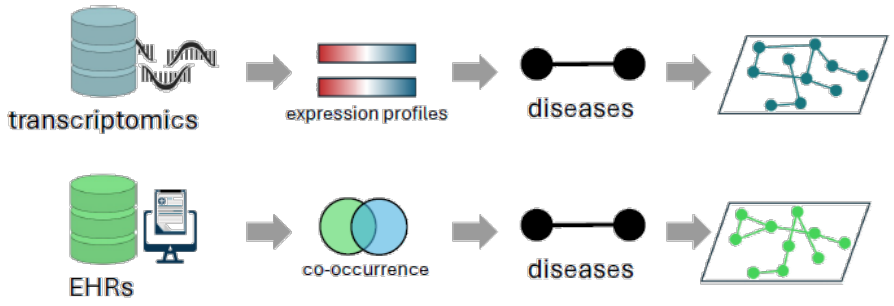

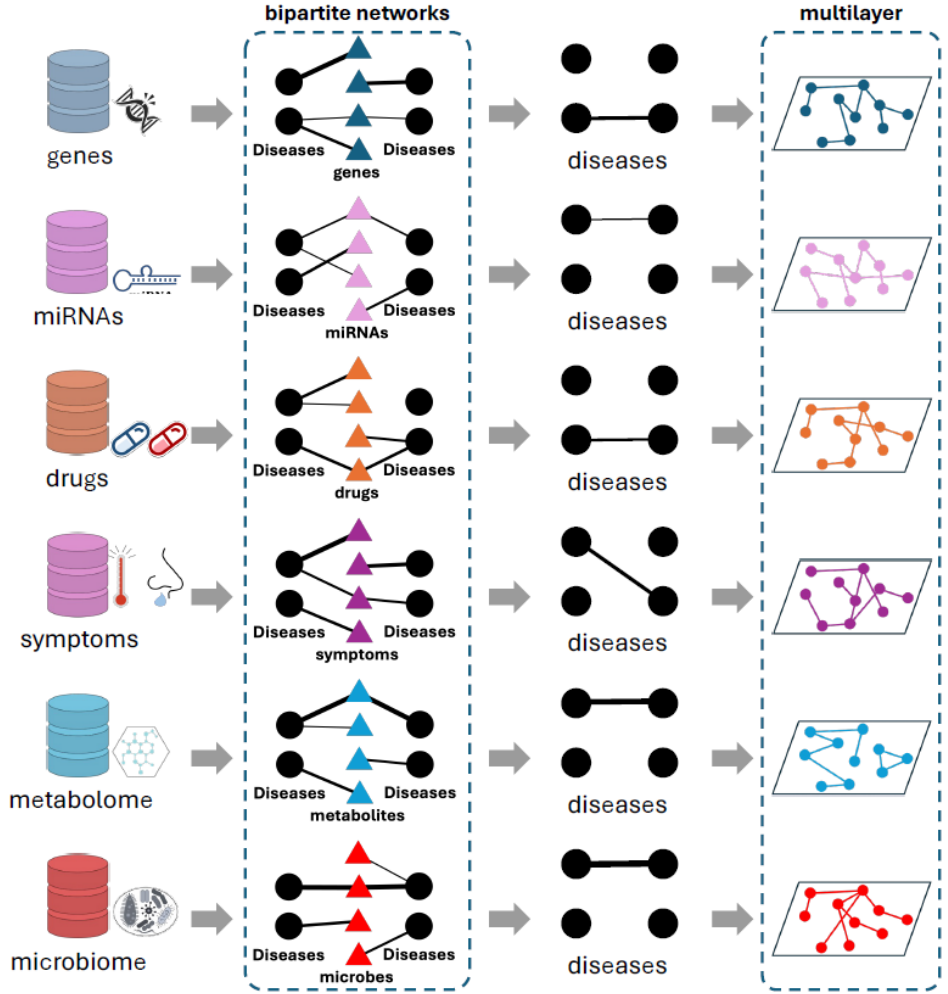

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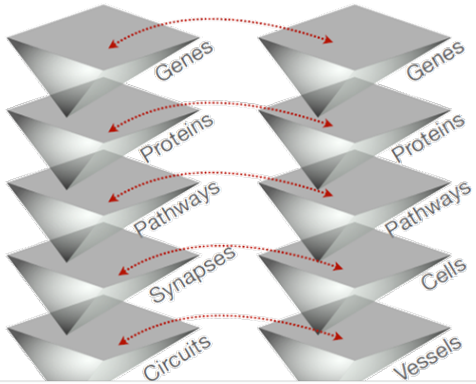

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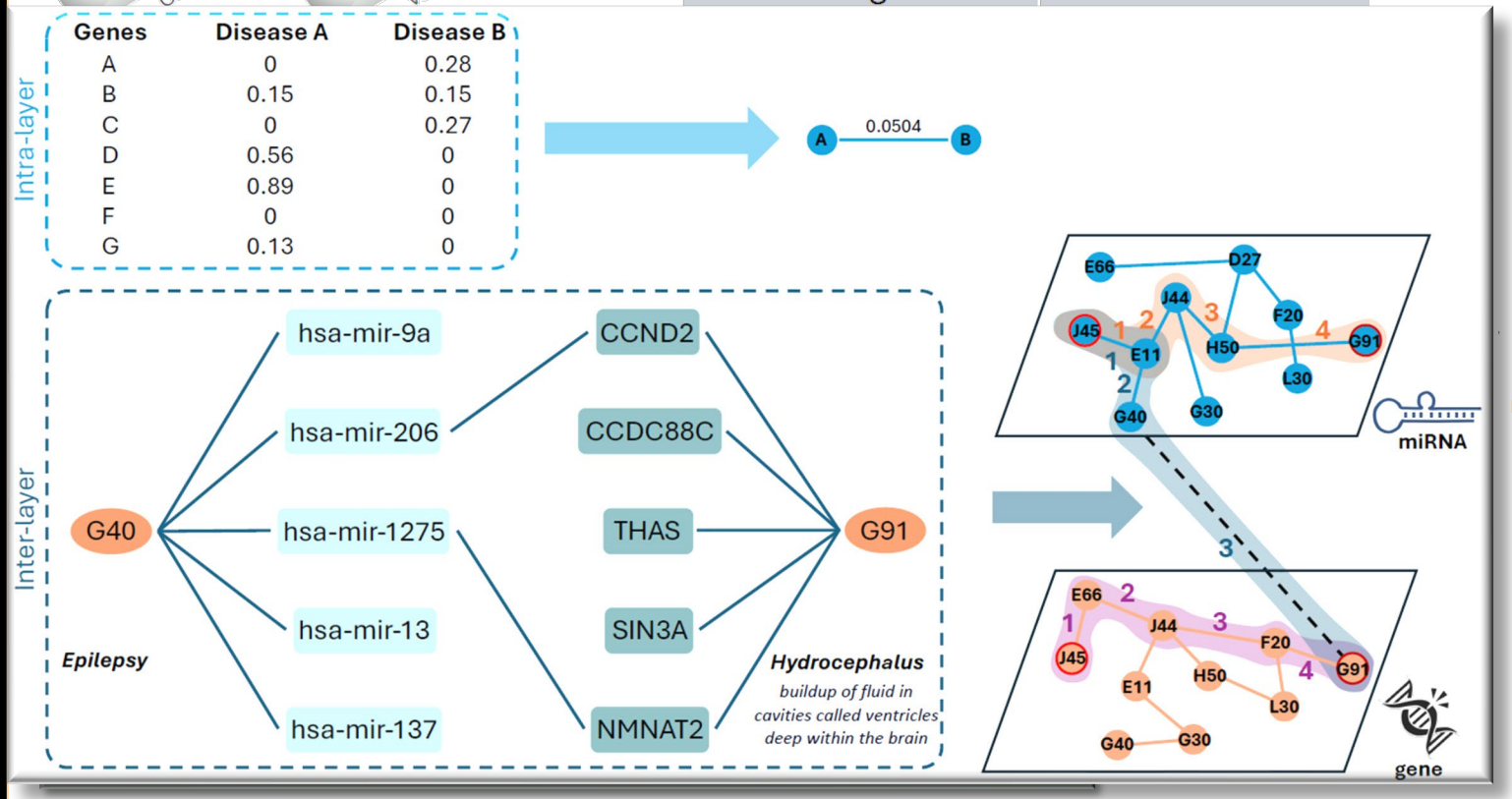

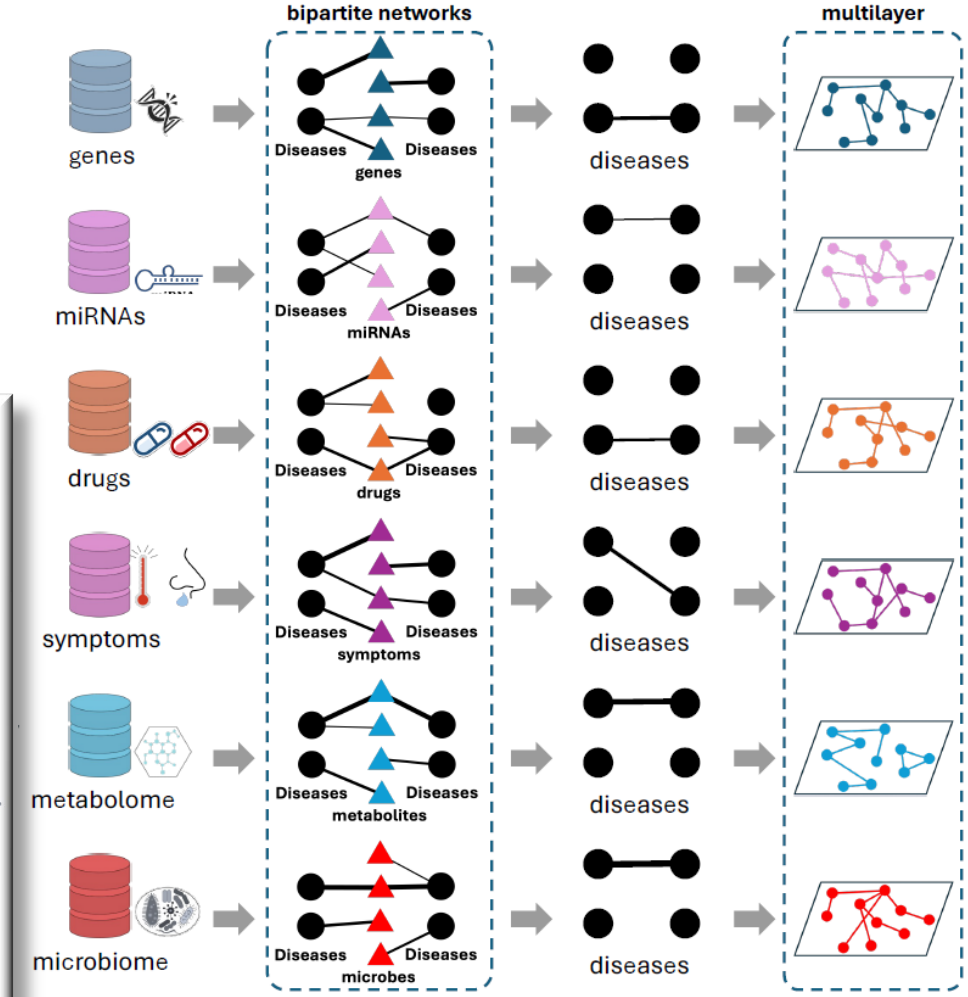

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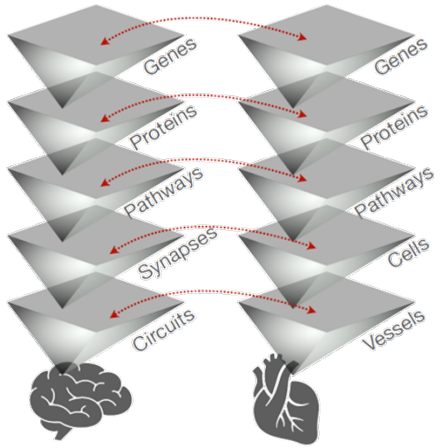
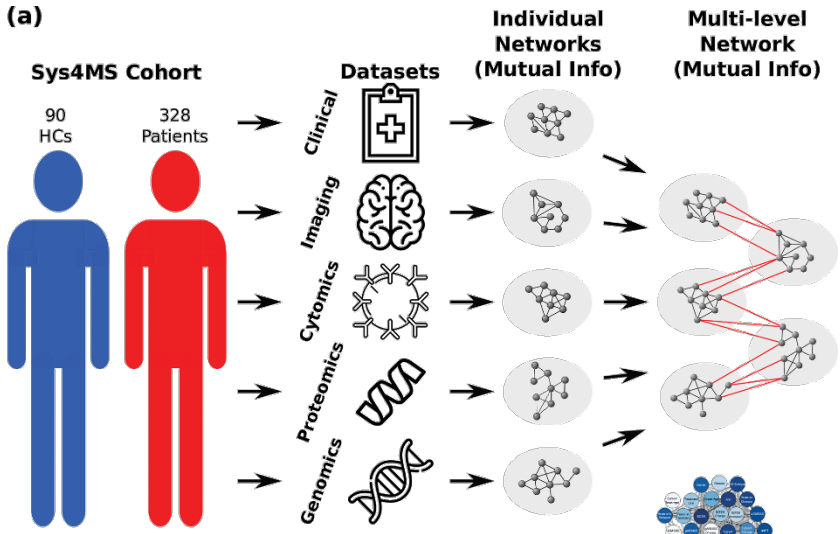
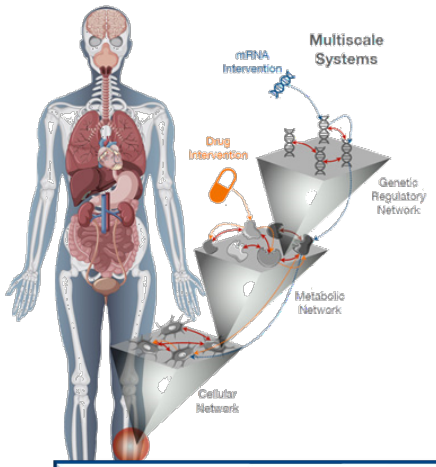
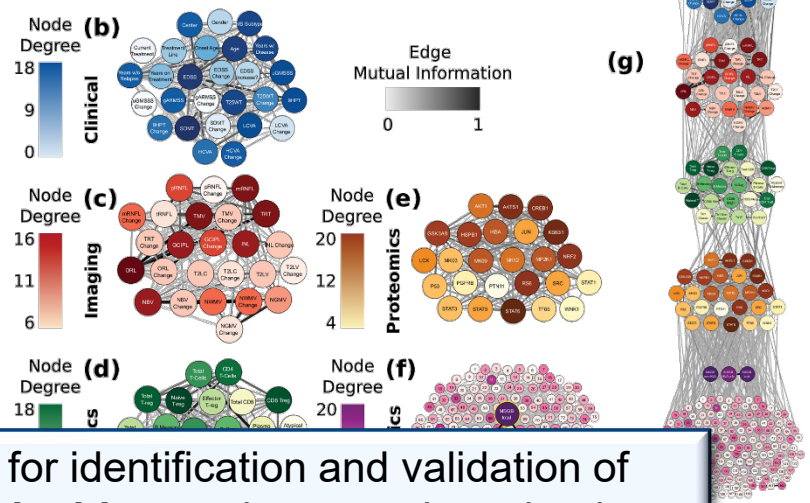
multilayer network models of multiscale factors in disease









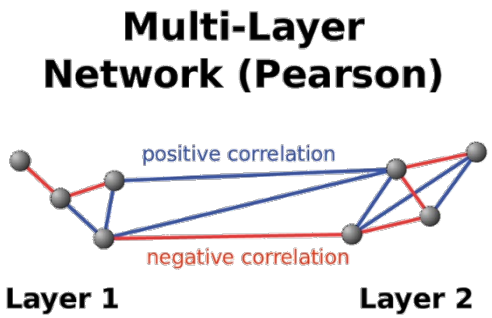
multilayer pathways for identification and validation of correlations and **explainable** putative causal mechanism: “lines of argumentation” for multiscale factors in disease

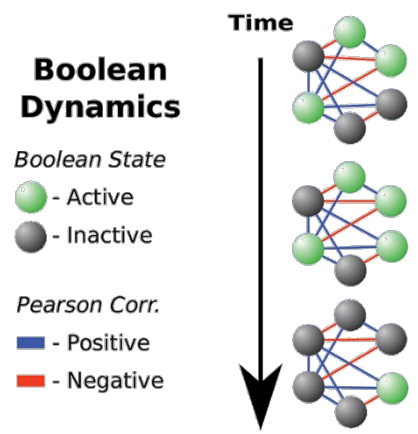
PLOS COMPUTATIONAL BIOLOGY

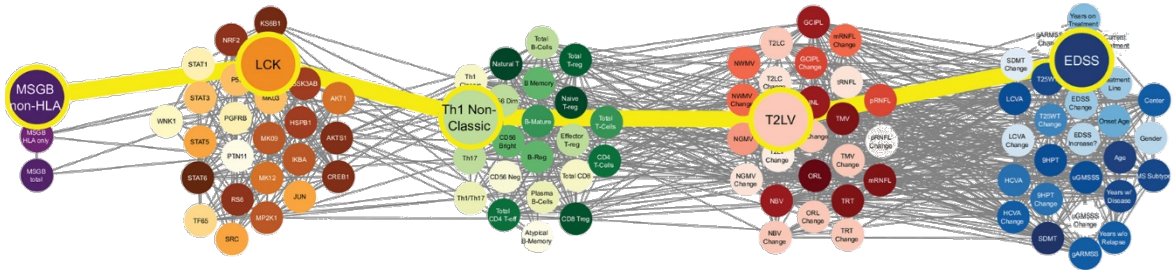
OPEN ACCESS PEER-REVIEWED
RESEARCH ARTICLE

Multiscale networks in multiple sclerosis

Keith E. Kennedy, Nicole Kerlero de Rosbo, Antonio Uccelli, Maria Cellerino, Federico Ivaldi, Paola Contini, Raffaele De Palma, Hanne F. Harbo, Tone Berge, Steffan D. Bos, Einar A. Høgestøl, Synne Brune-Ingebretsen, Sigrid A. de Rodez Benavent, [---], Pablo Villoslada [view all]







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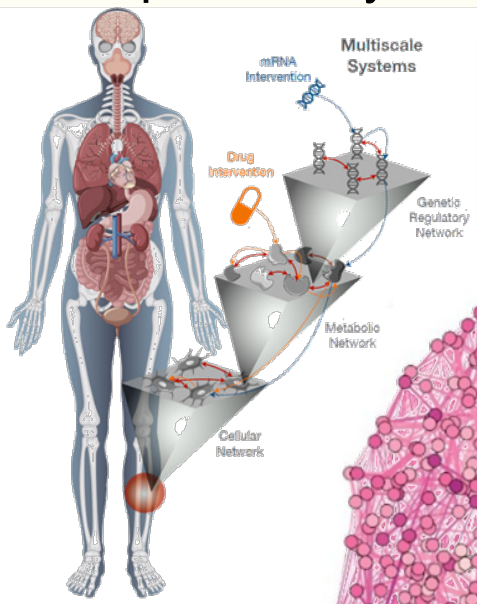
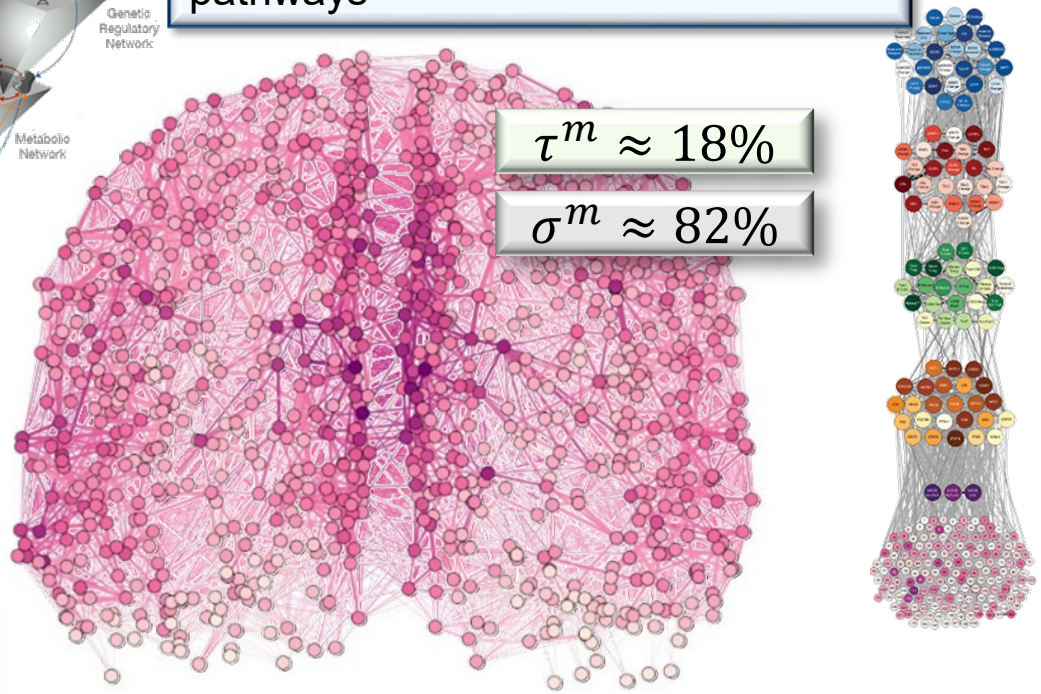
simplifying multilevel complexity by extracting redundancy

for explainability and computability



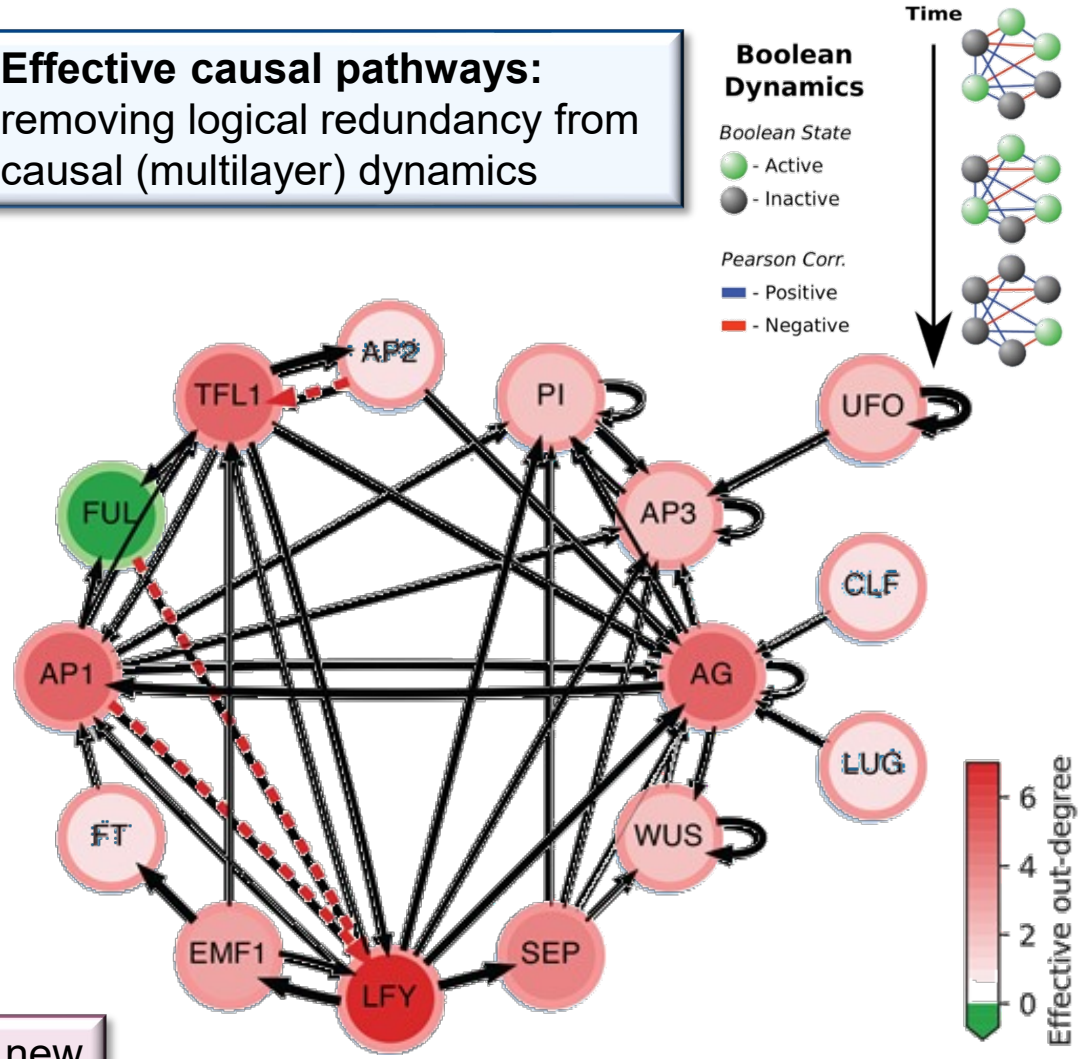
distance backbones of networks: removing redundancy from (shortest) pathways



$\tau^m \approx 18\%$

$\sigma^m \approx 82\%$

Effective causal pathways: removing logical redundancy from causal (multilayer) dynamics



Howard Pattee

functional (control) hierarchies (especially symbolic codes) establish a “selective loss of detail”.

handles for interventions: If there is emergence of new levels, there must be ***redundancy*** for control to work.

Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.

Simas, Correia & Rocha [2021]. *J Complex Networks*. **9** (6), cnab021.

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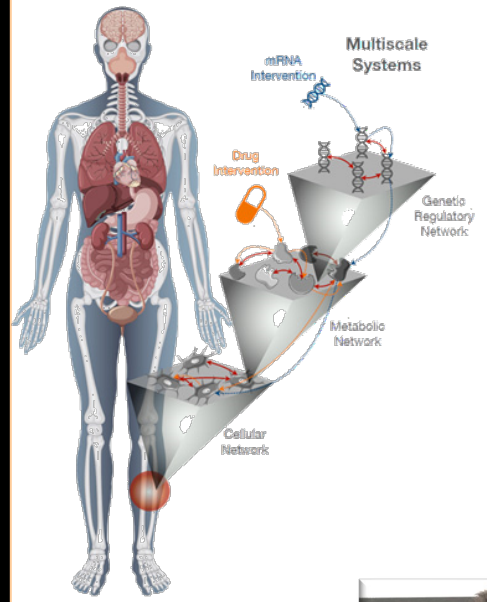
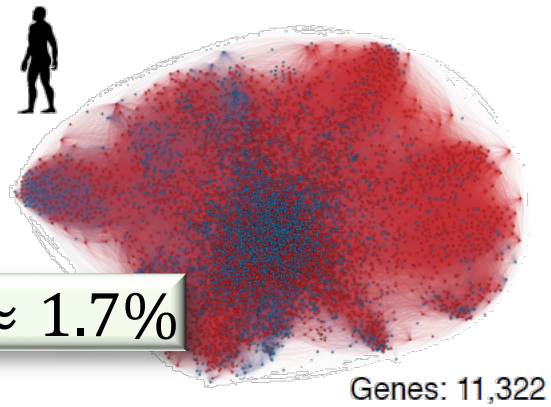
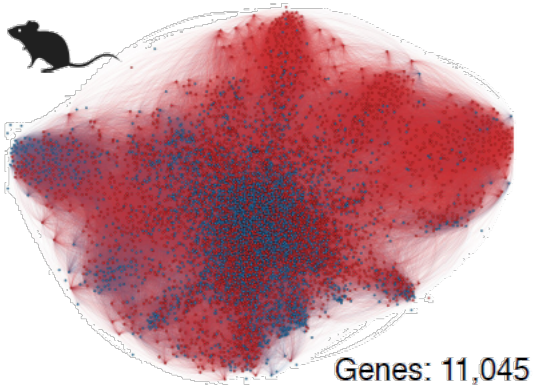
distance backbone helps uncovers ancient regulators of human spermatogenesis

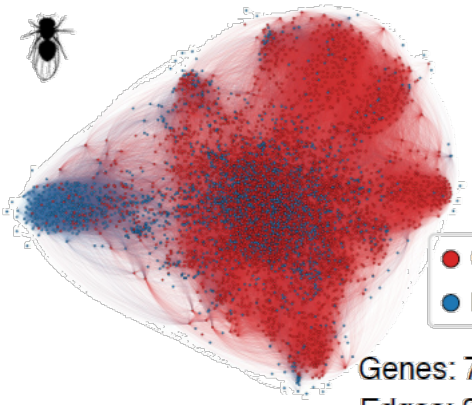


$\tau^m \approx 1.7\%$

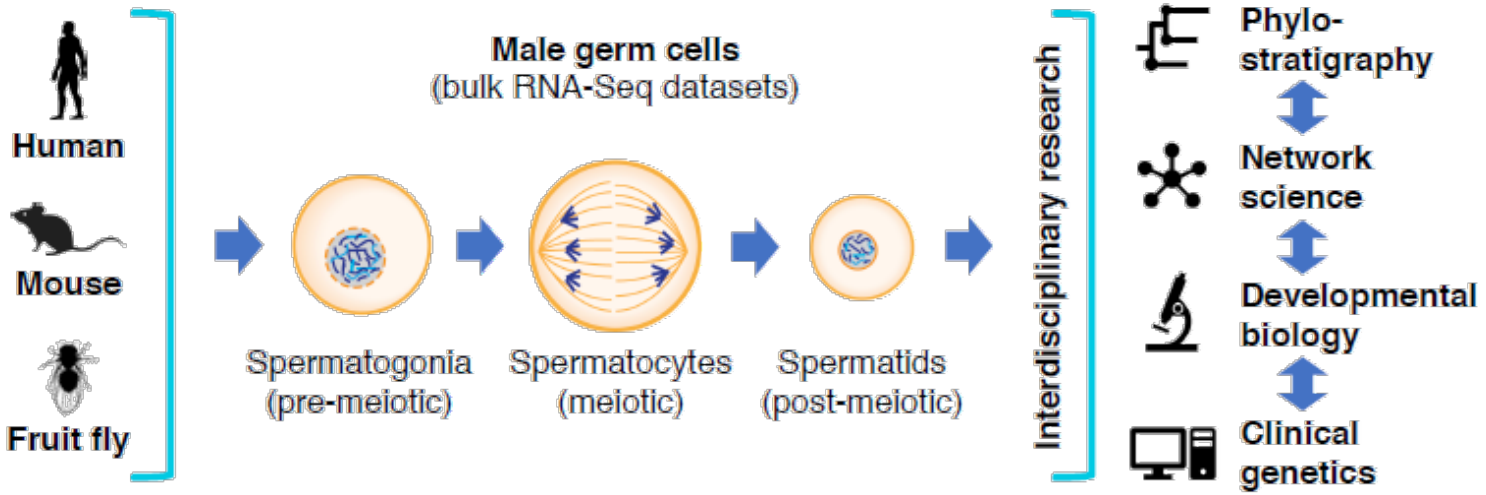
Meiotic transcriptome networks


Genes: 11,322
Edges: 351,250


Genes: 11,045
Edges: 326,129


Genes: 7,961
Edges: 225,729

Conserved gene
Non-conserved gene



Correia et al [2024]. *eLife*. **13**:RP95774
Correia, Barrat & Rocha [2023]. *PLoS Computational Biology*. **19**(2): e1010854.
Simas, Correia & Rocha [2021]. *J Complex Networks*. **9** (6), cnab021.

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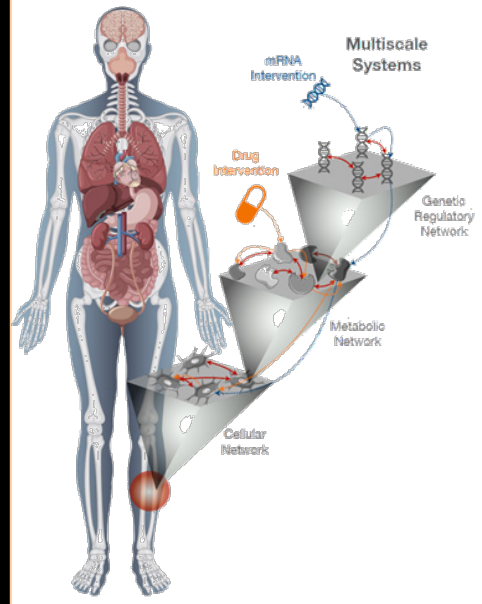

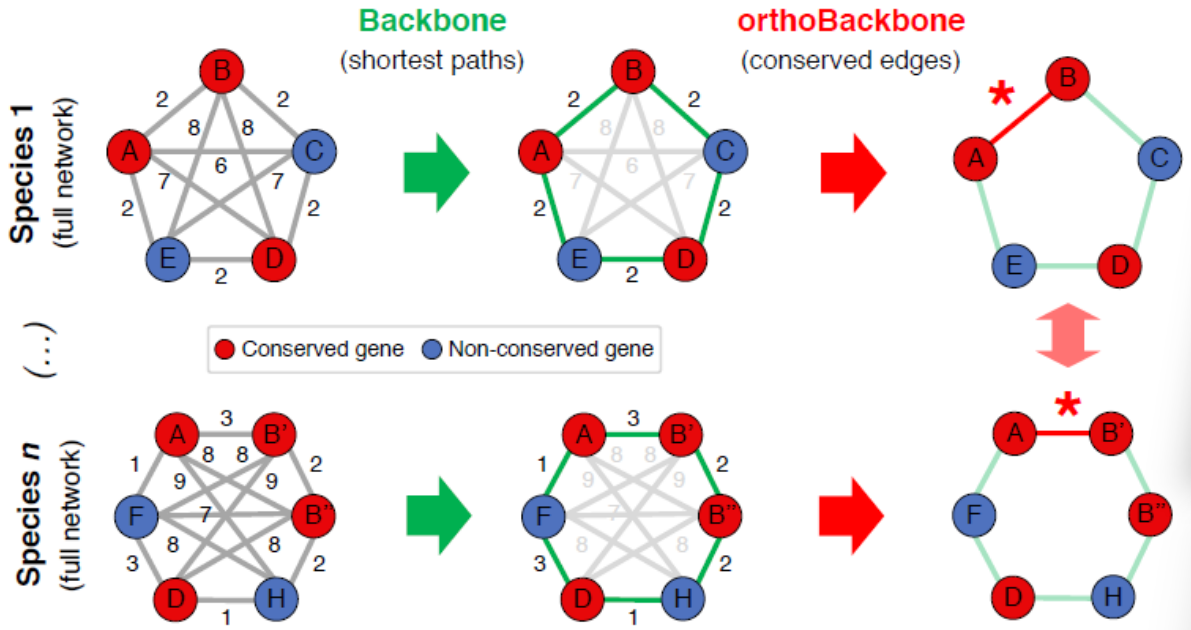

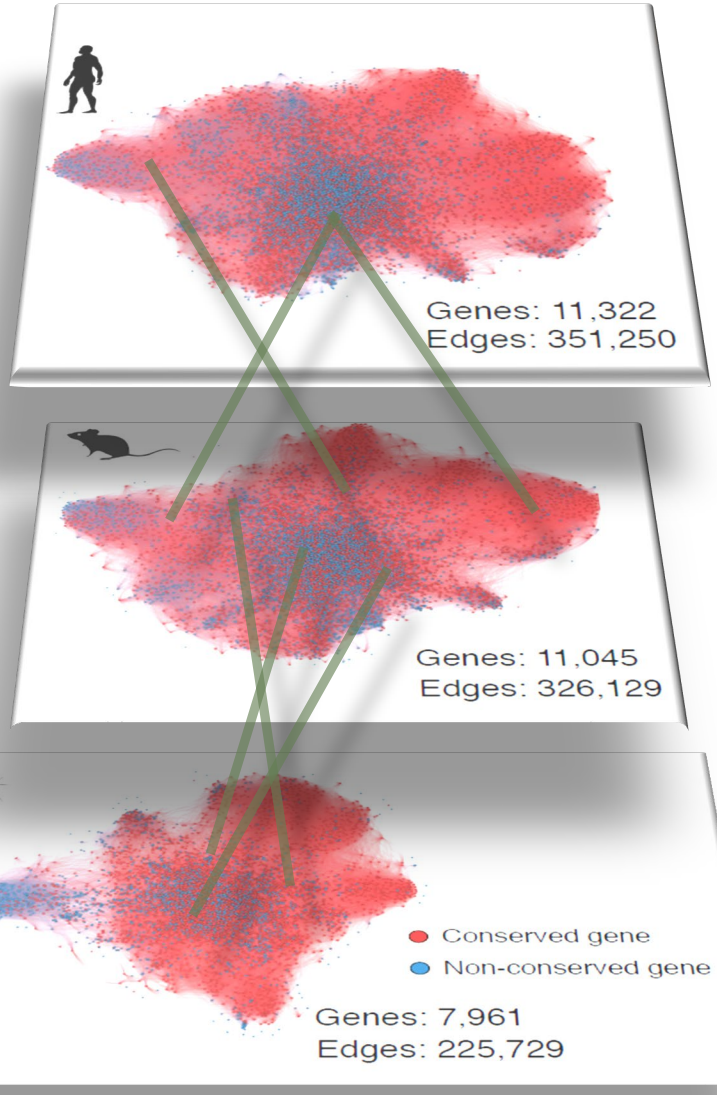

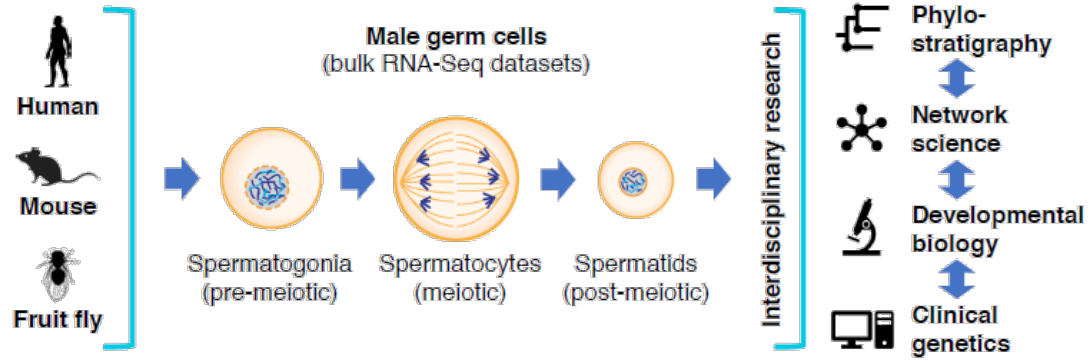

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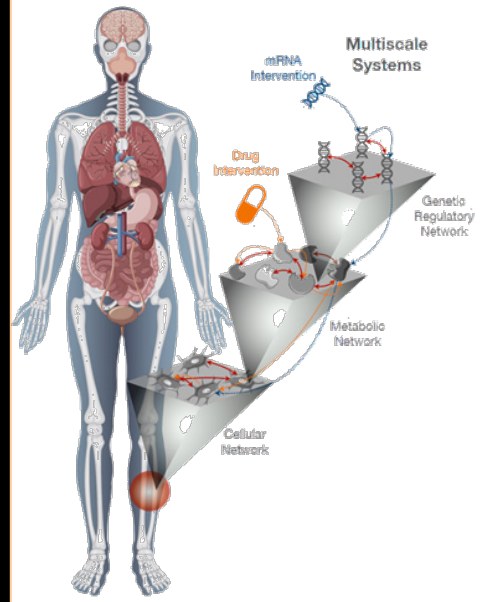
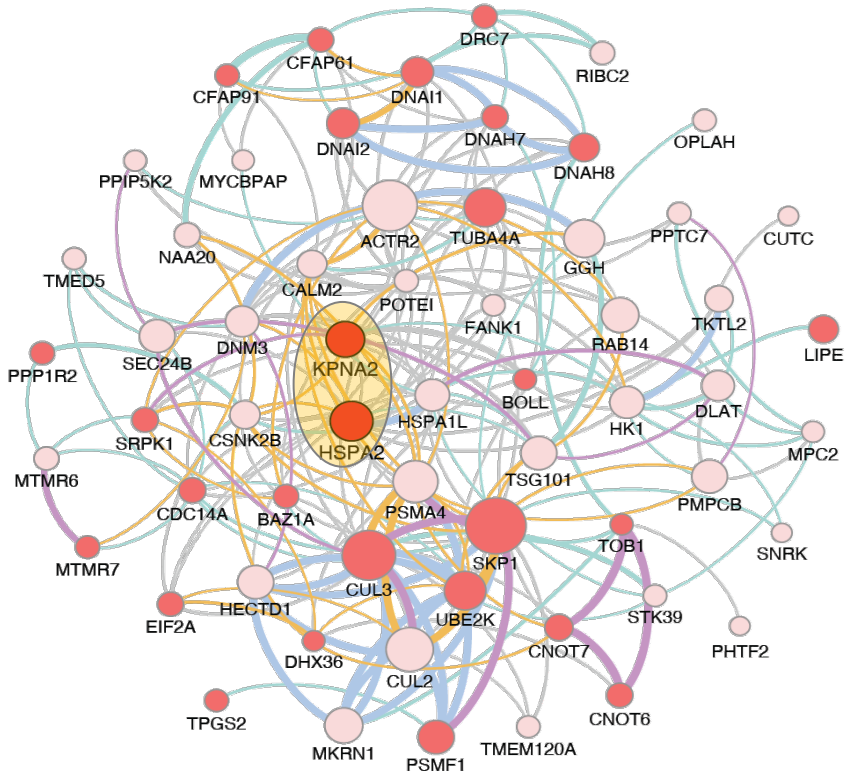




Nodes

Page Rank 4.3x10-4 0.2x10-4

Spermatogenic function?

Published

Unknown

Edges

Score 0.99 0.15

Main source of information

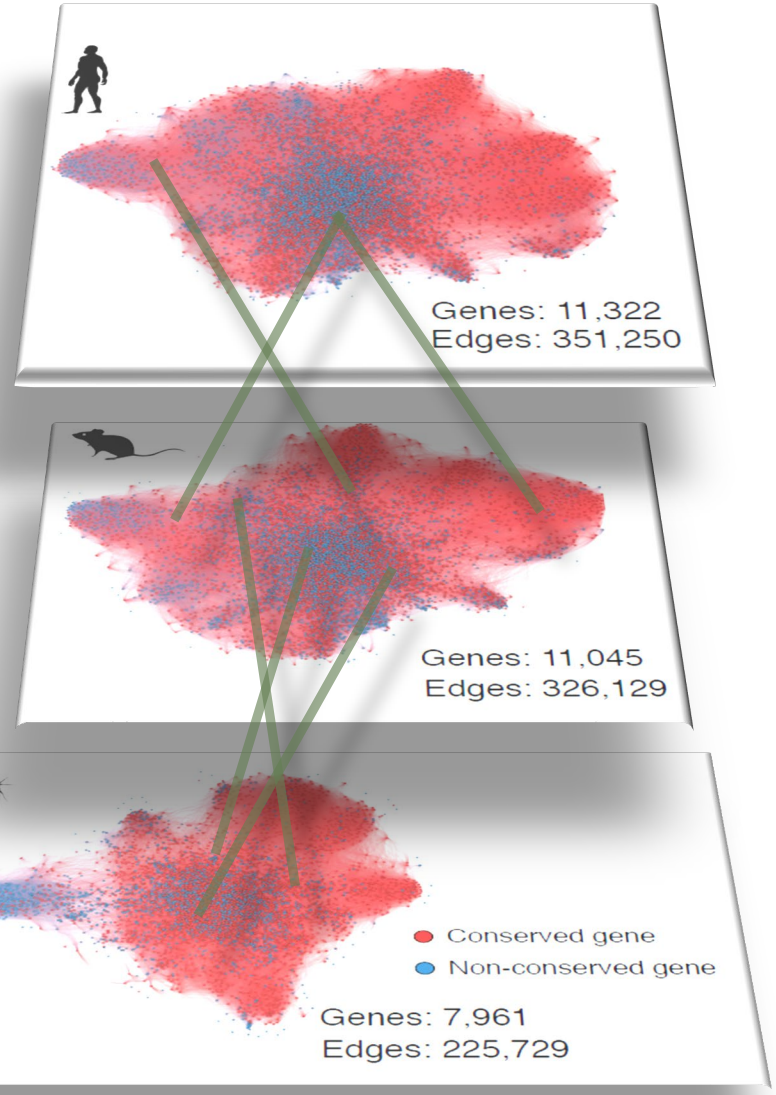
Experiments

Co-expression

Databases

Text mining

Other



Paulo Navarro-Costa U. Lisboa Medical School

Correia et al [2024]. *eLife*. **13**:RP95774

complete loss of germ cells with HSPA2 and KPNA2 variants

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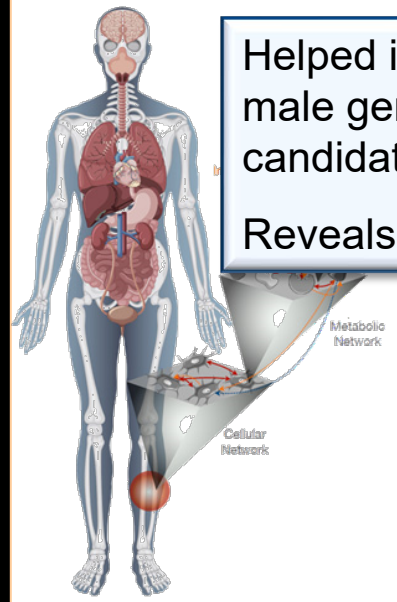
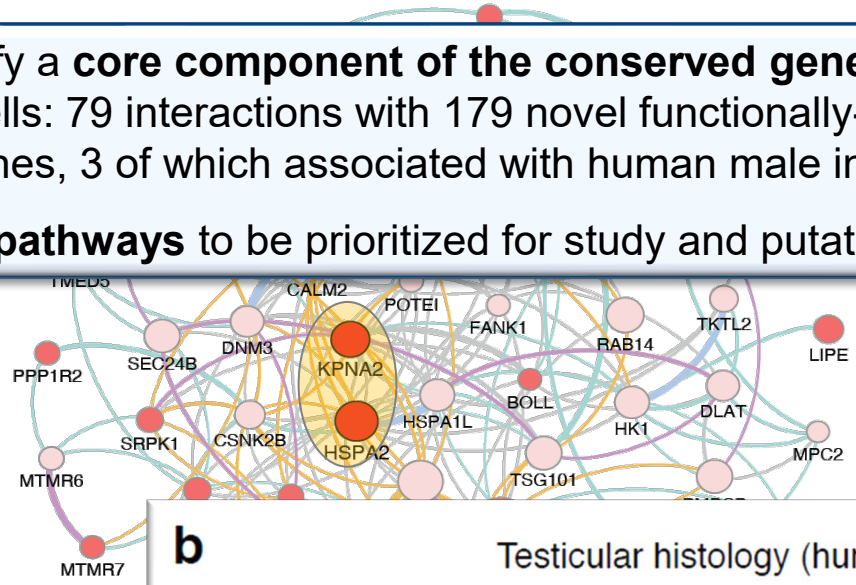
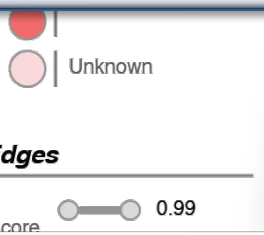
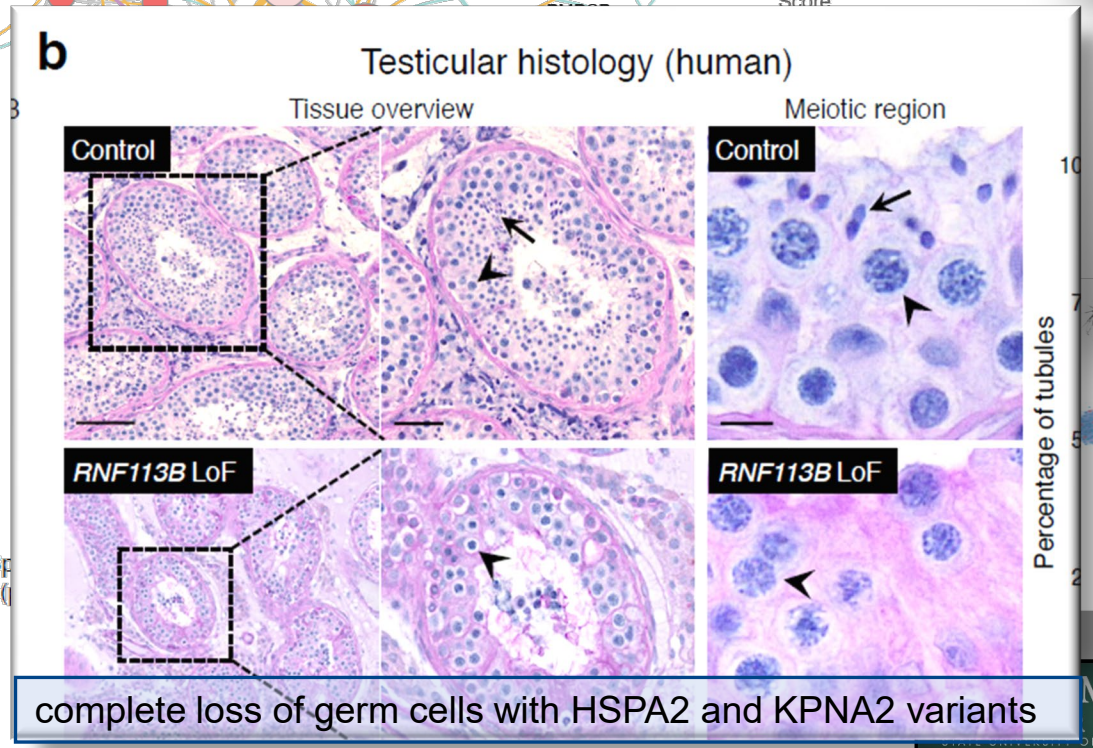


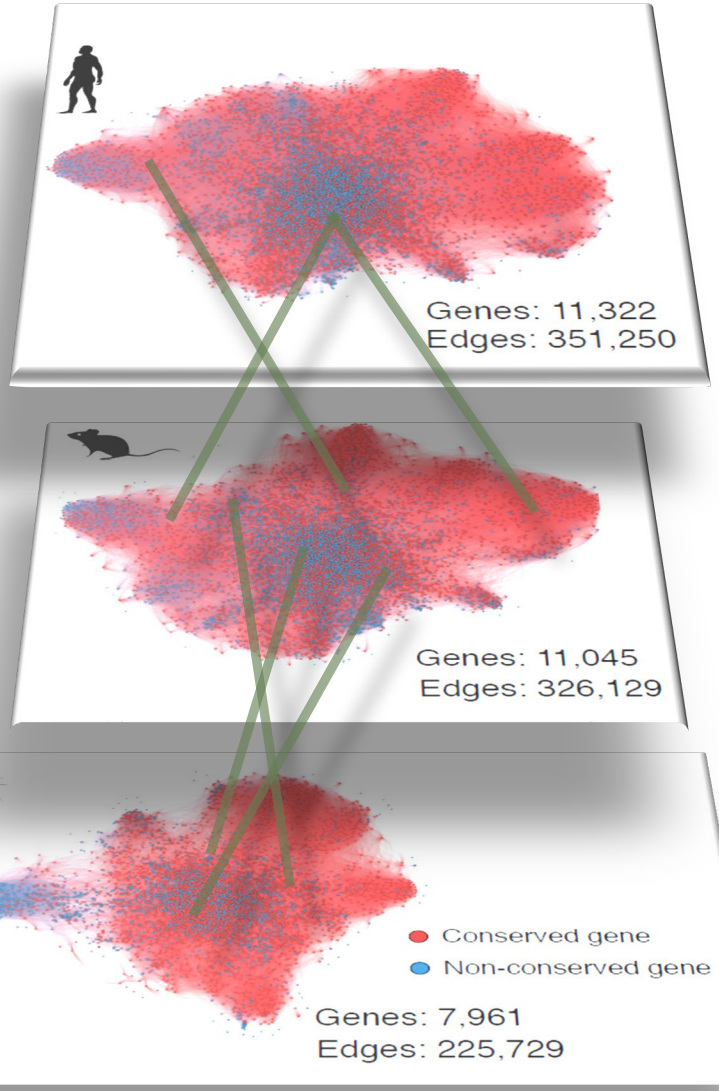
Helped identify a **core component of the conserved genetic program** of male germ cells: 79 interactions with 179 novel functionally-validated candidate genes, 3 of which associated with human male infertility.

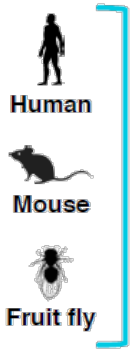
Reveals **key pathways** to be prioritized for study and putative interventions.











complete loss of germ cells with HSPA2 and KPNA2 variants

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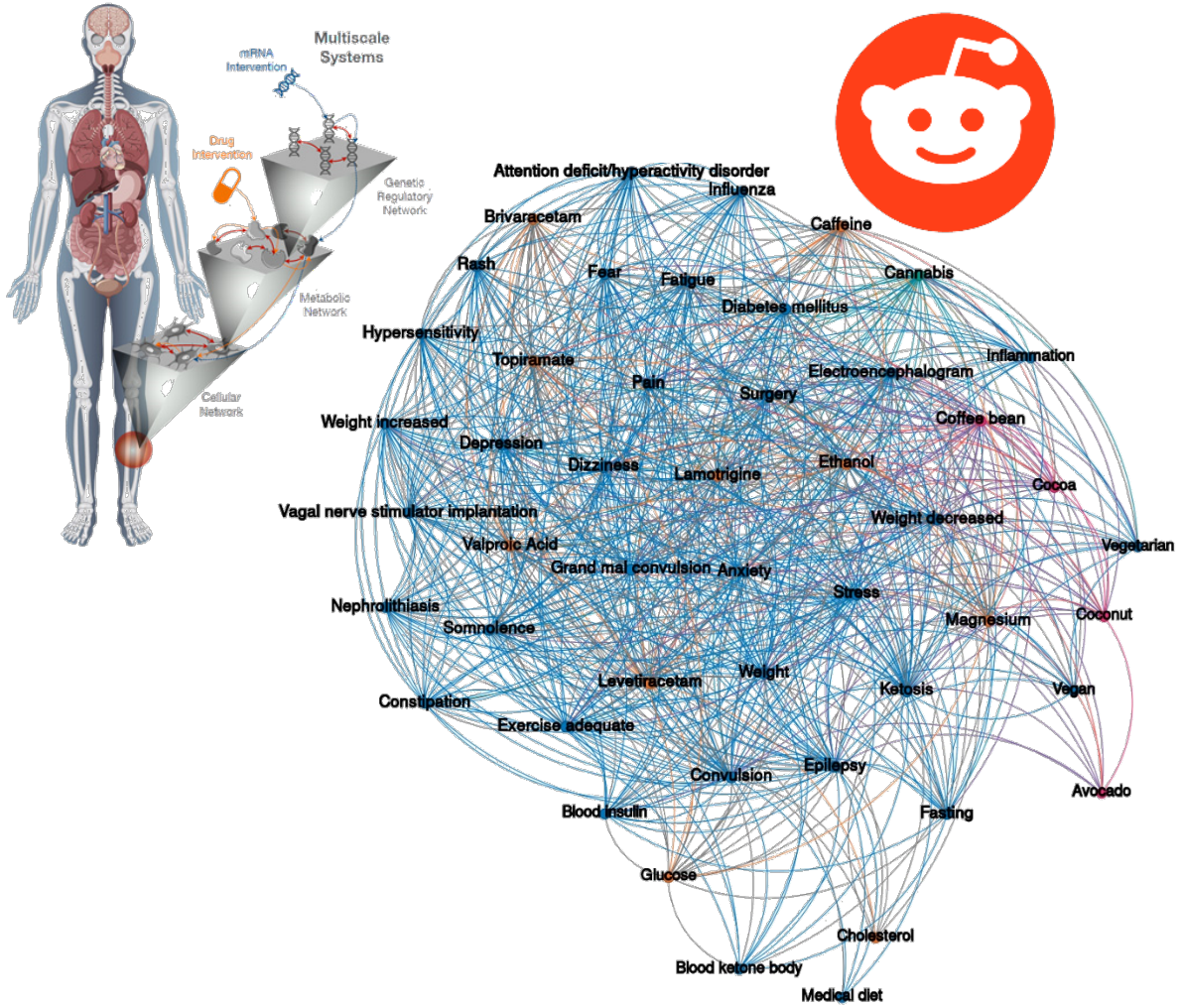
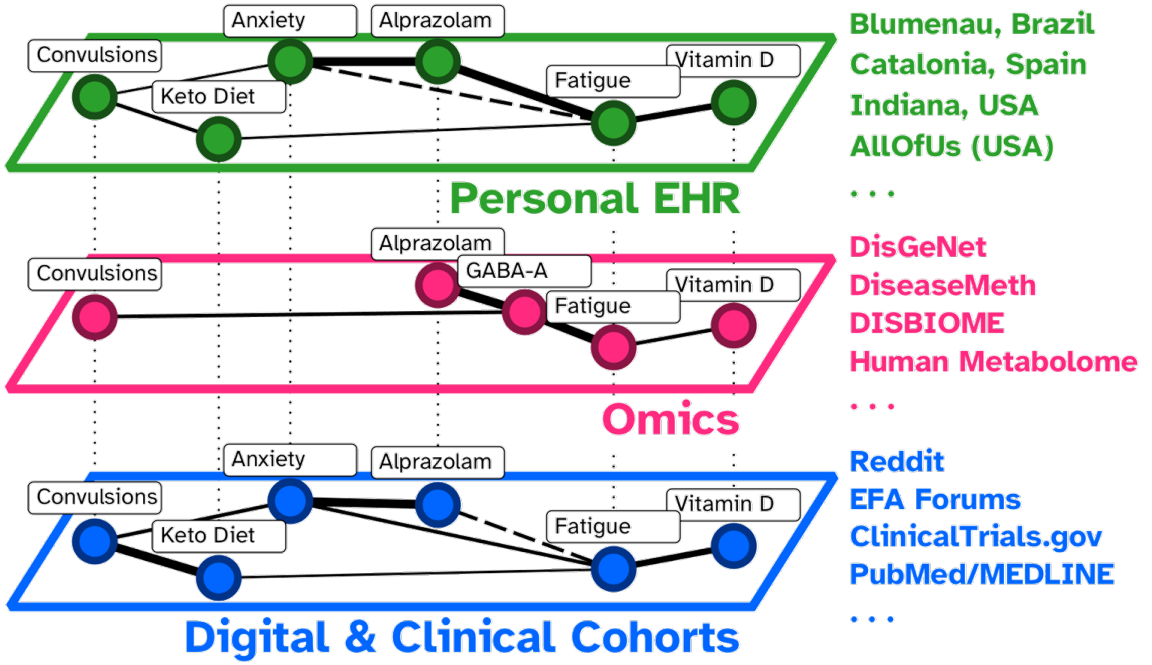
Correia et al [2024]. *eLife*. **13**:RP95774

myAURA 2.0: uncovering and explaining multiscale factors in disease

integrating multiomics, human health data and exposome layers





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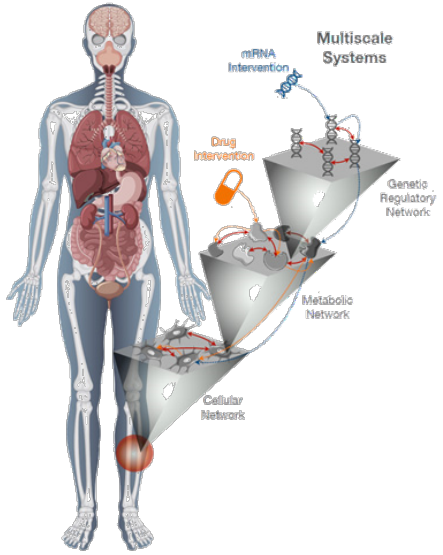

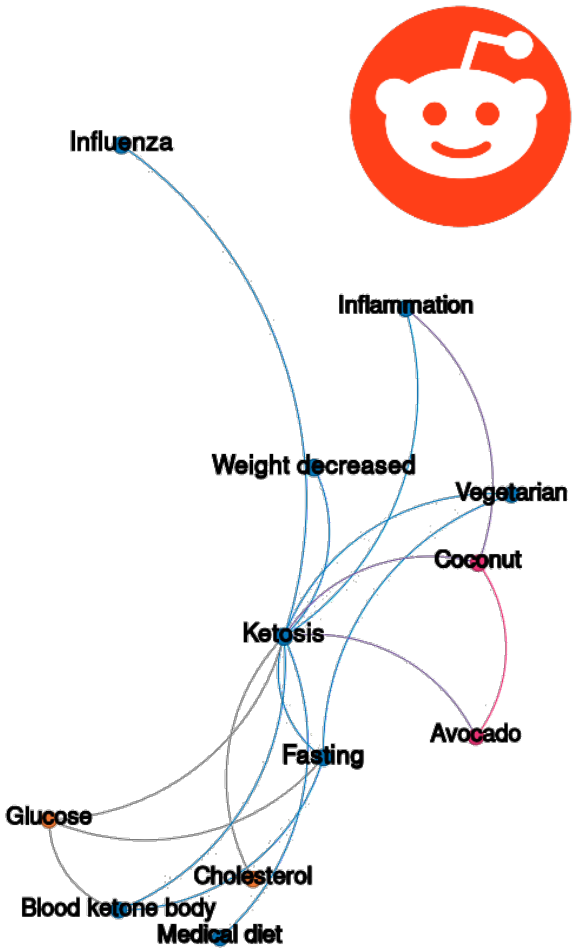

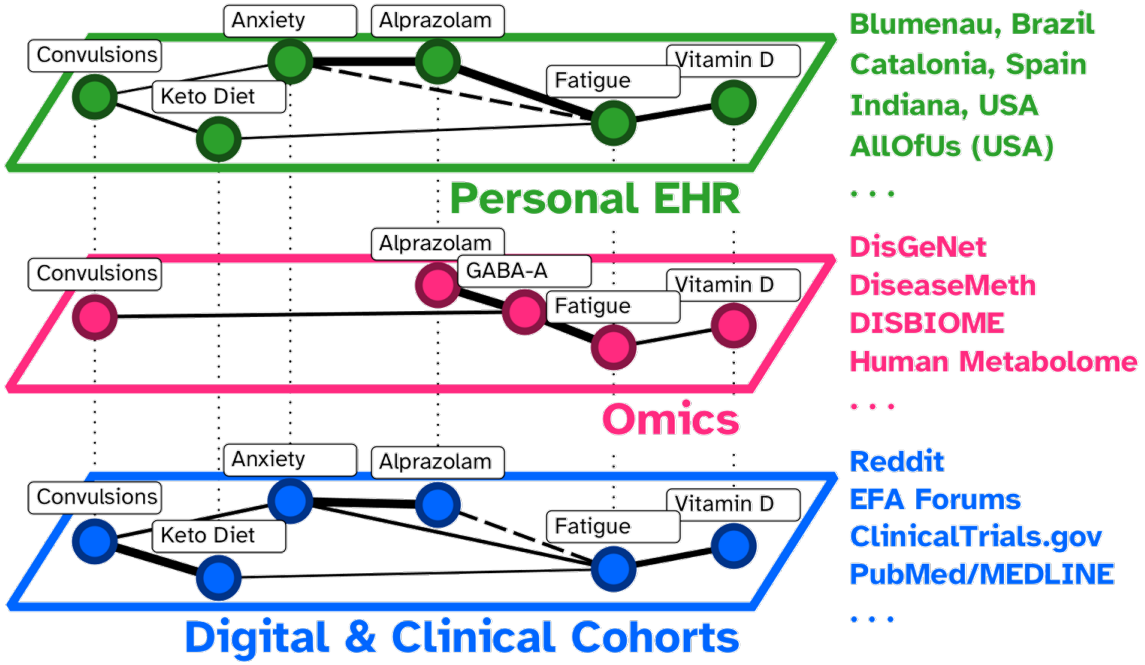

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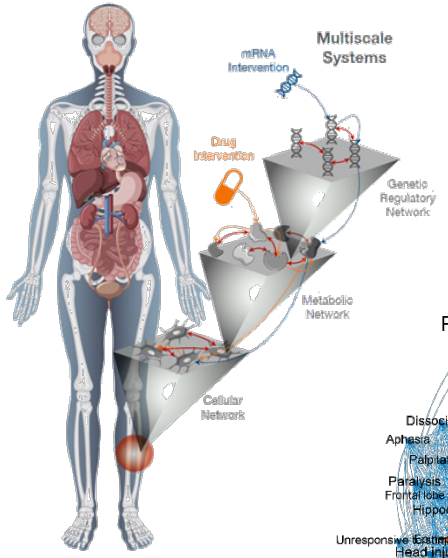

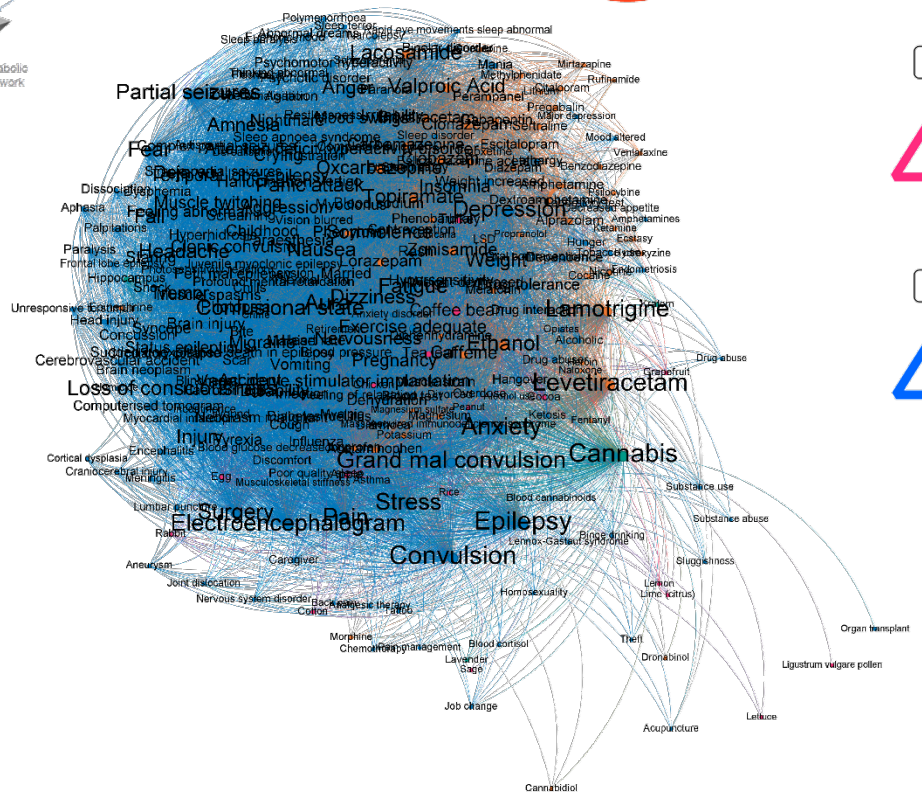

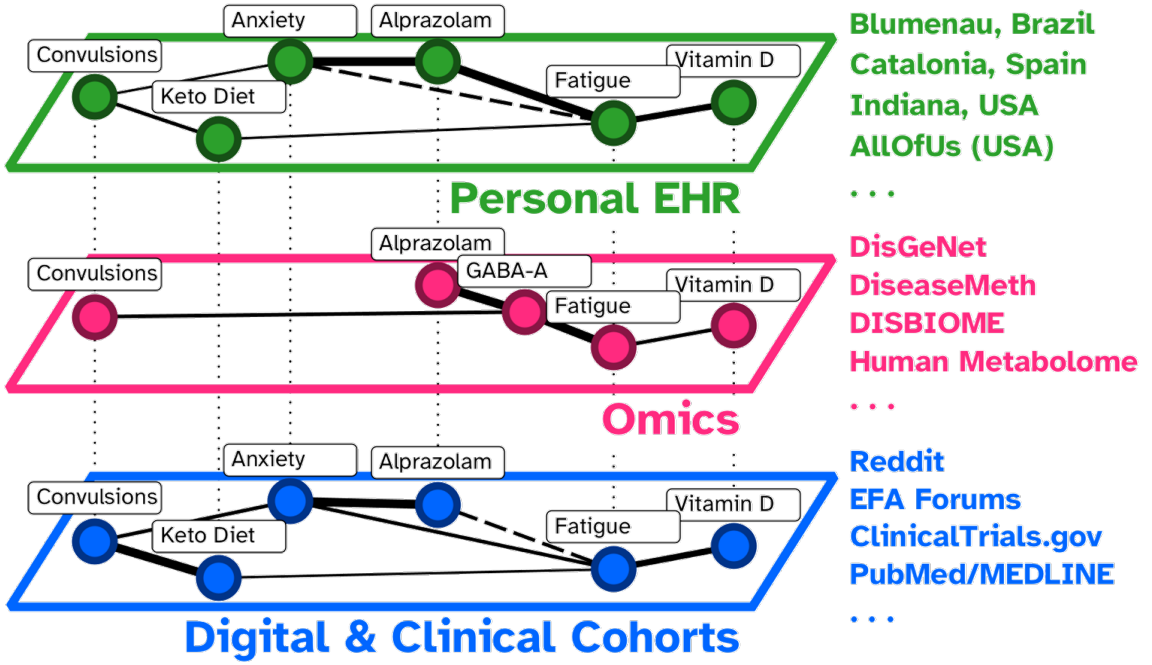

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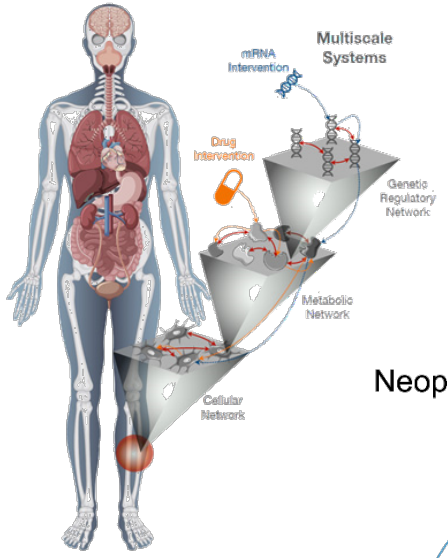

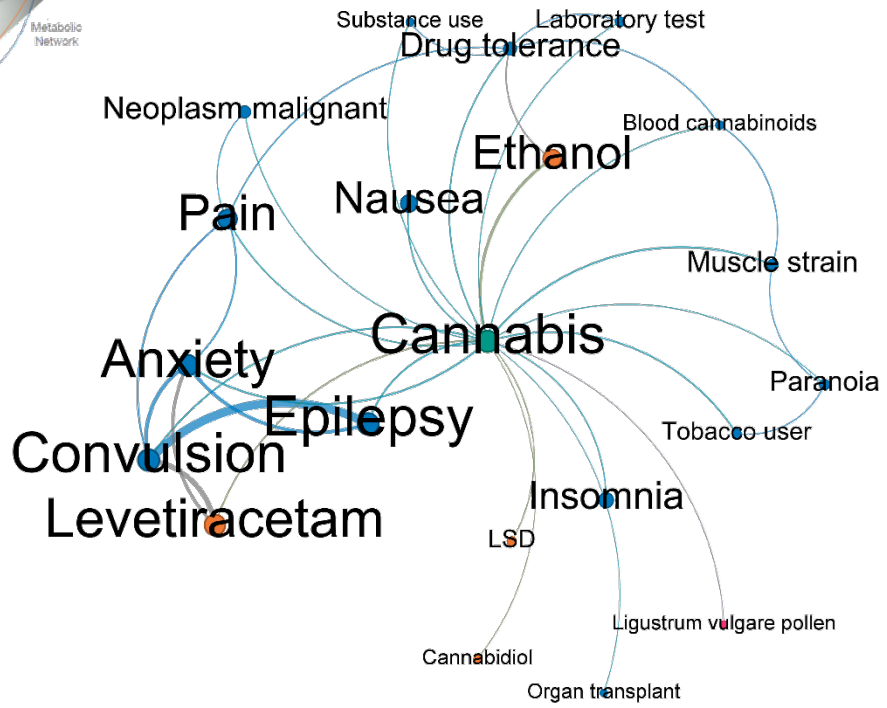

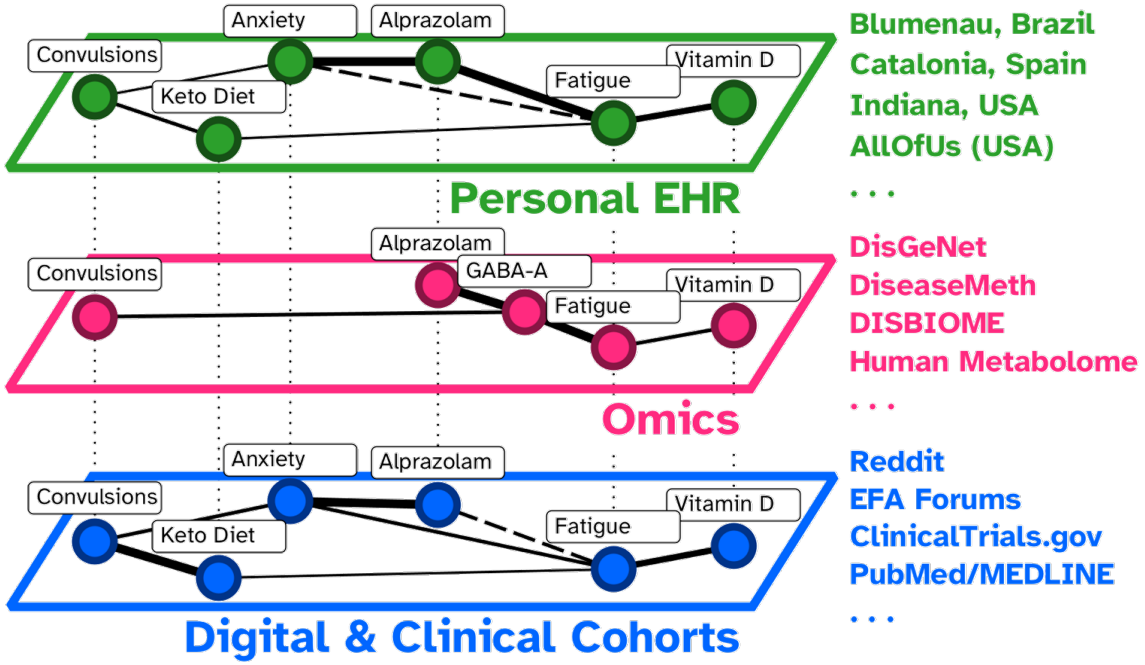

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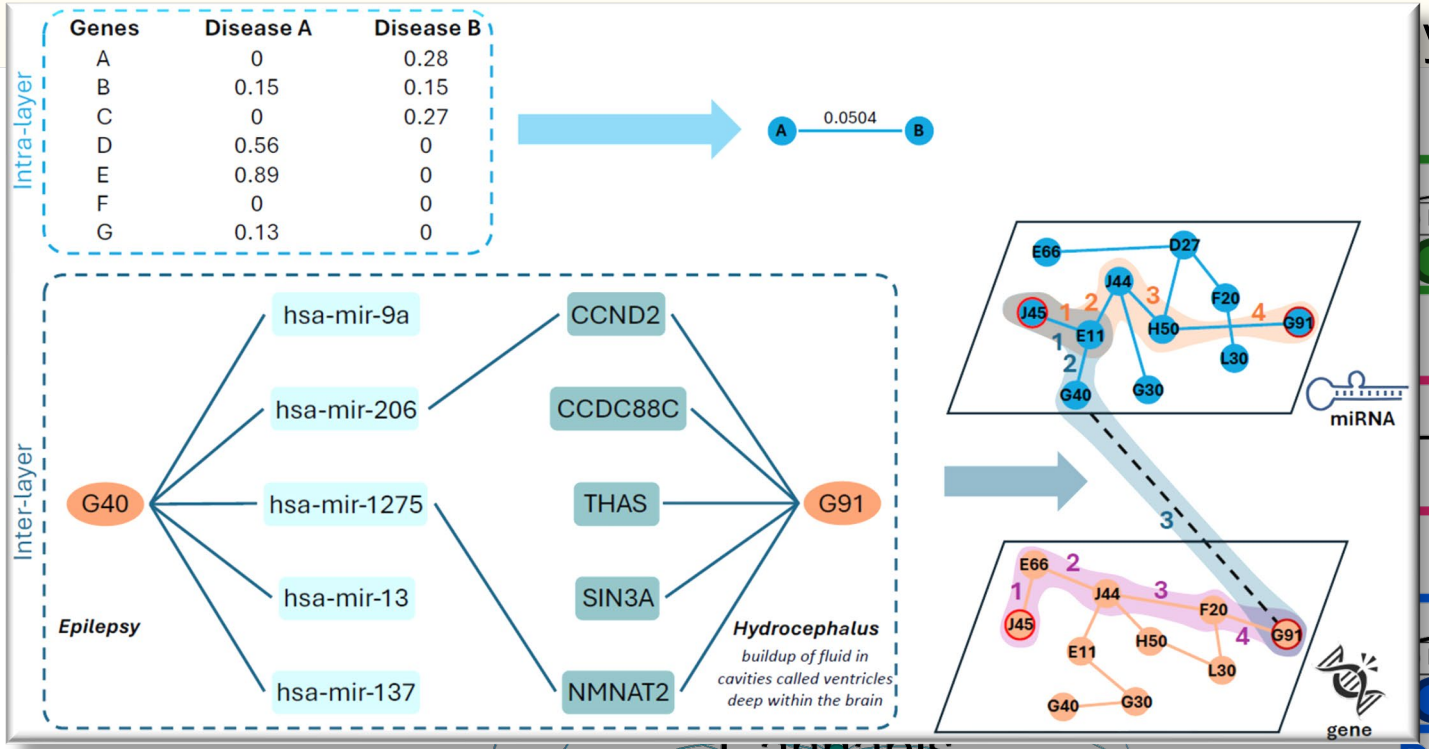

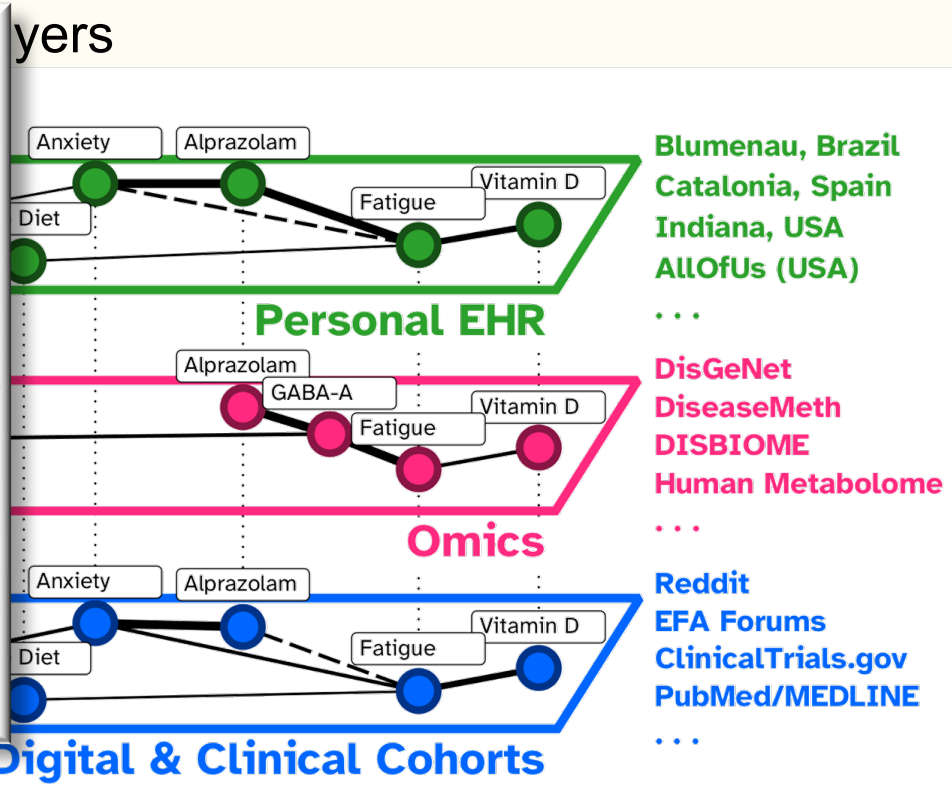

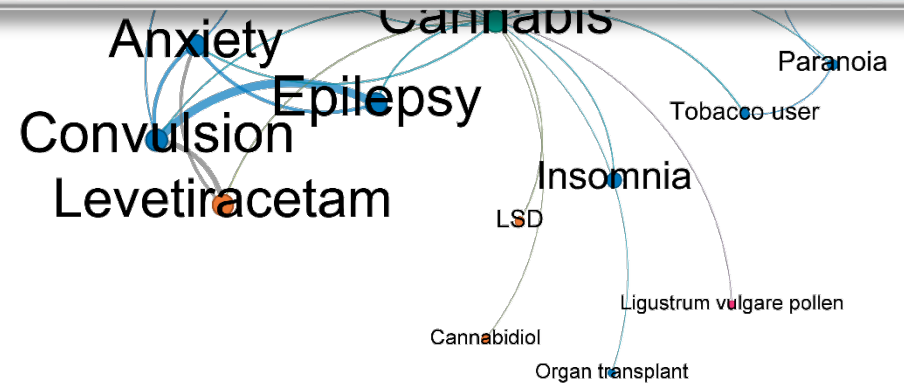

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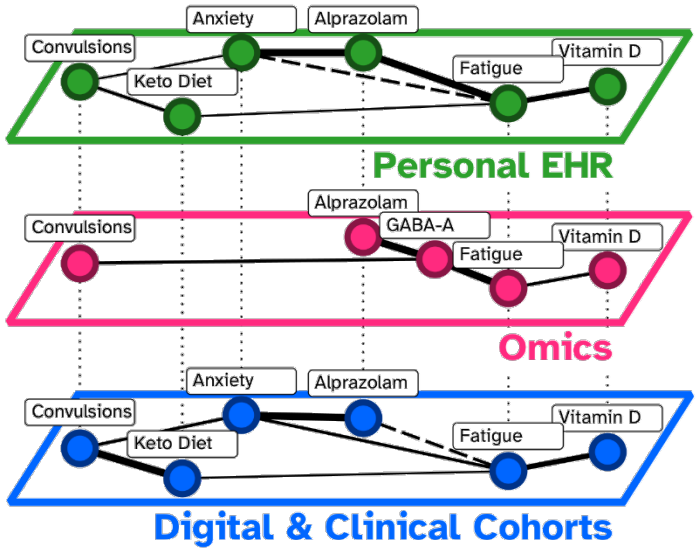
myAURA 2.0: uncovering (and explaining) multiscale factors in disease

analyzing multilayer distance backbone via causal (logical) models

removal of redundancy from multilayer pathways between multiomics and exposome layers **facilitates explanation** of multiscale factors in disease



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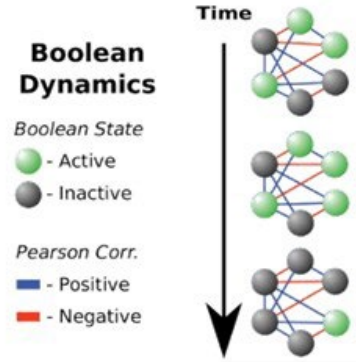

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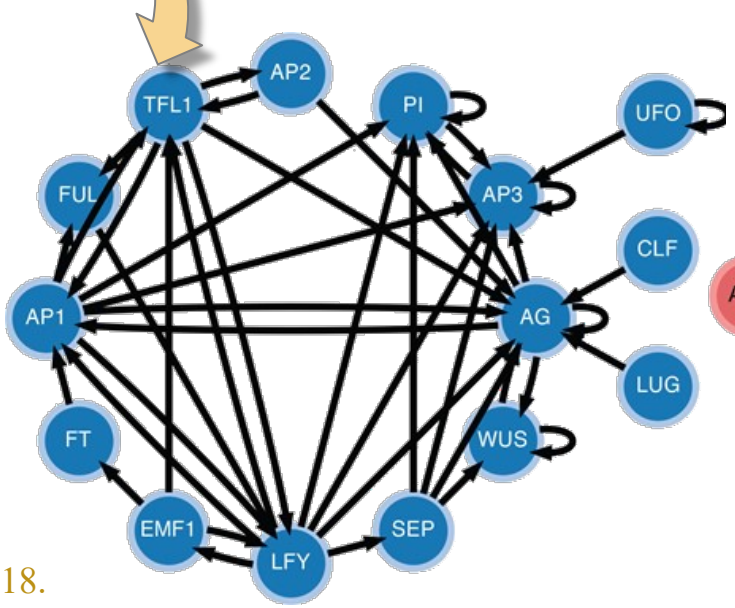
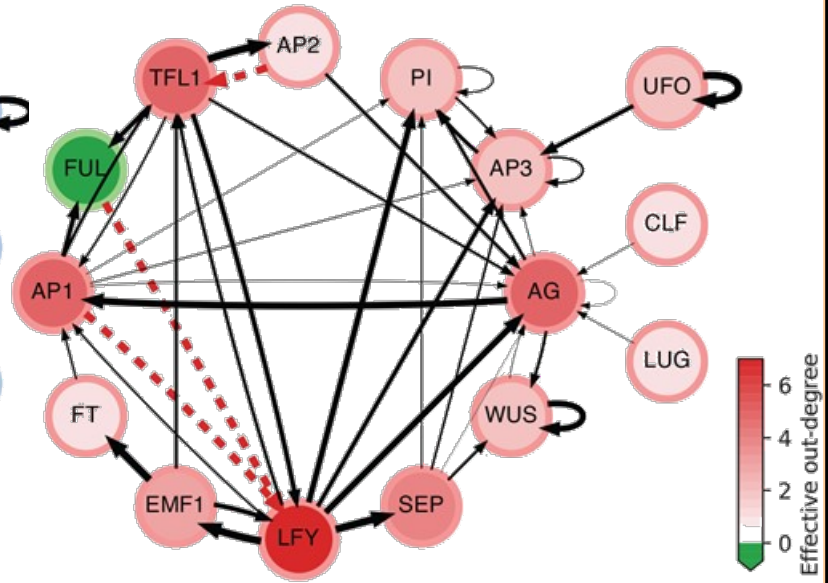
RESEARCH ARTICLE

Multiscale networks in multiple sclerosis

Keith E. Kennedy, Nicole Kerlero de Rosbo, Antonio Uccelli, Maria Cellerino, Federico Ivaldi, Paola Contini, Raffaele De Palma, Hanne F. Harbo, Tone Berge, Steffan D. Bos, Einar A. Høgestøl, Synne Brune-Ingebretsen, Sigrid A. de Rodez Benavent, [...], Pablo Villoslada [view all]

Effective causal pathways: removing logical redundancy from causal (multilayer) dynamics





Multilayer distance backbones of networks: removing redundancy from (shortest) pathways

Marques-Pita & Rocha, [2013]. *PLoS ONE*, **8**(3): e55946.
Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.
Rozum & Rocha [2024]. *Journal of Physics: Complexity*. ad679e.
Simas, Correia & Rocha [2021]. *J Complex Networks*. **9** (6), cnab021.

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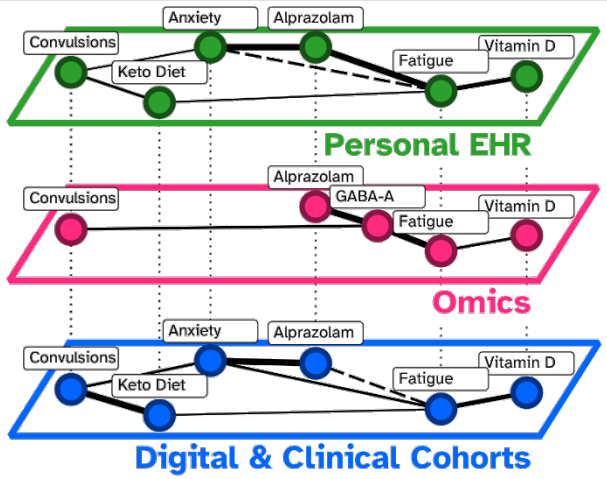

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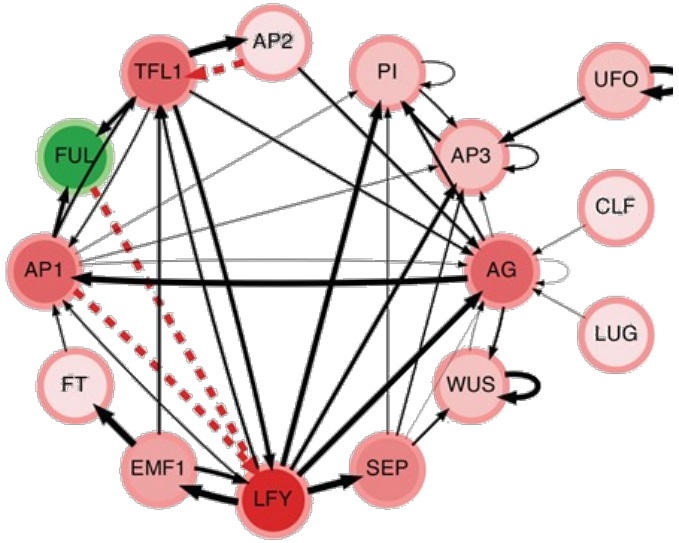

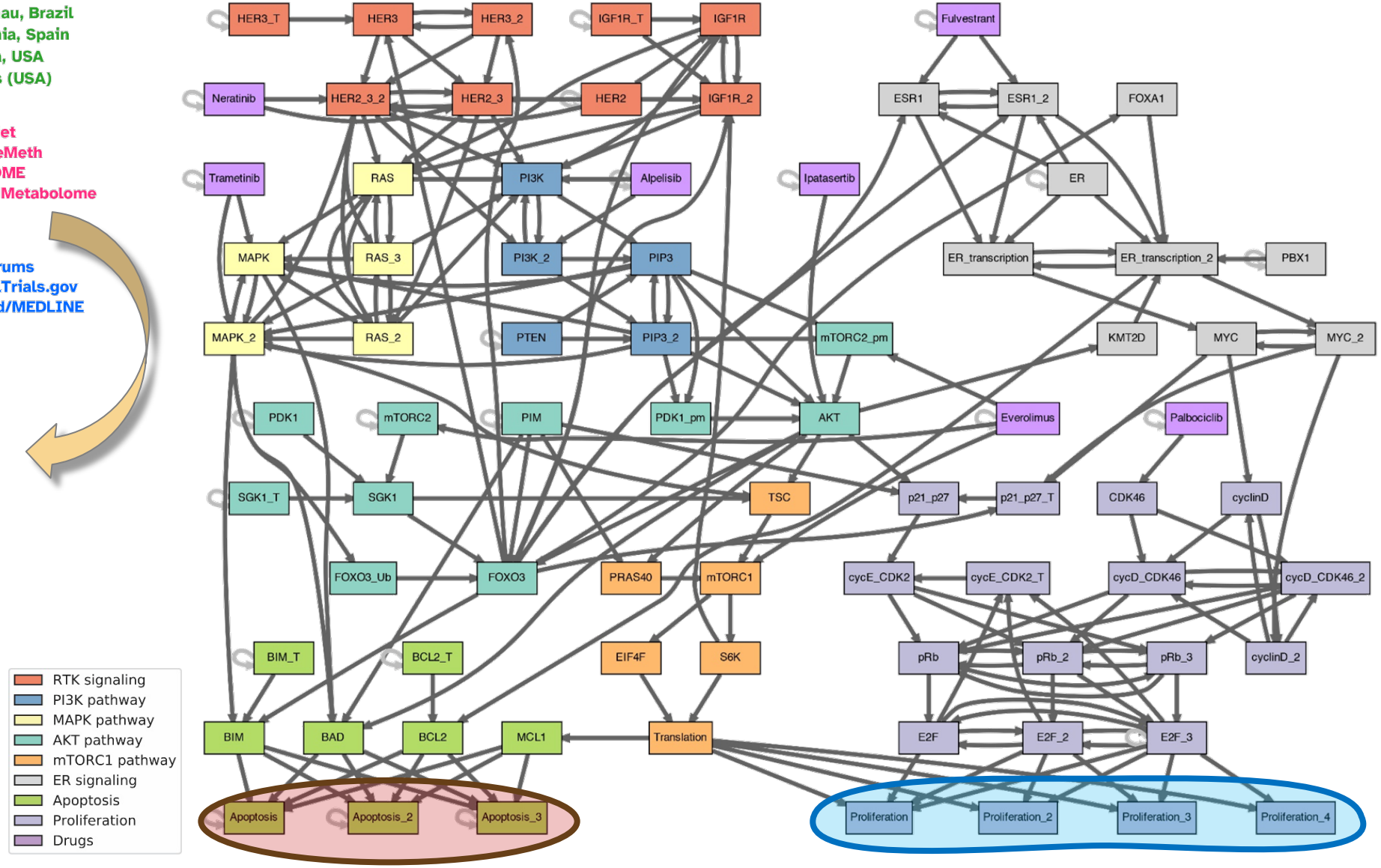

RTK signaling
PI3K pathway
MAPK pathway
AKT pathway
mTORC1 pathway
ER signaling
Apoptosis
Proliferation
Drugs

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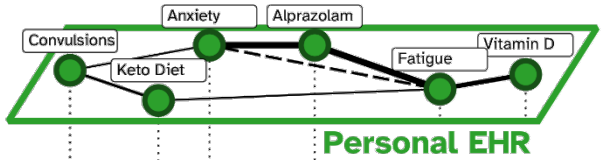

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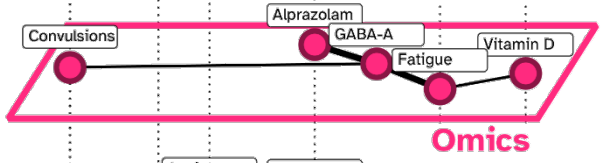

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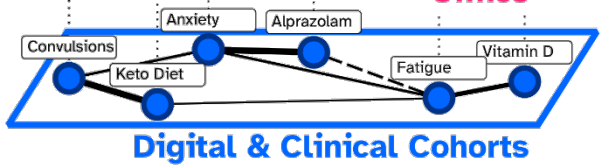

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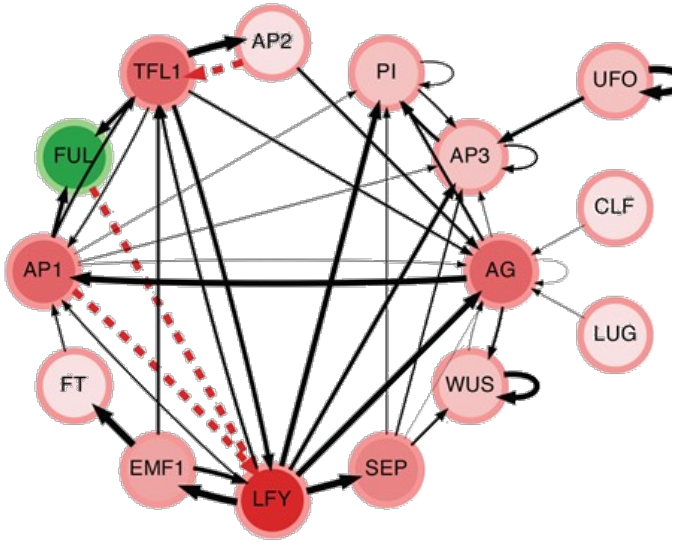

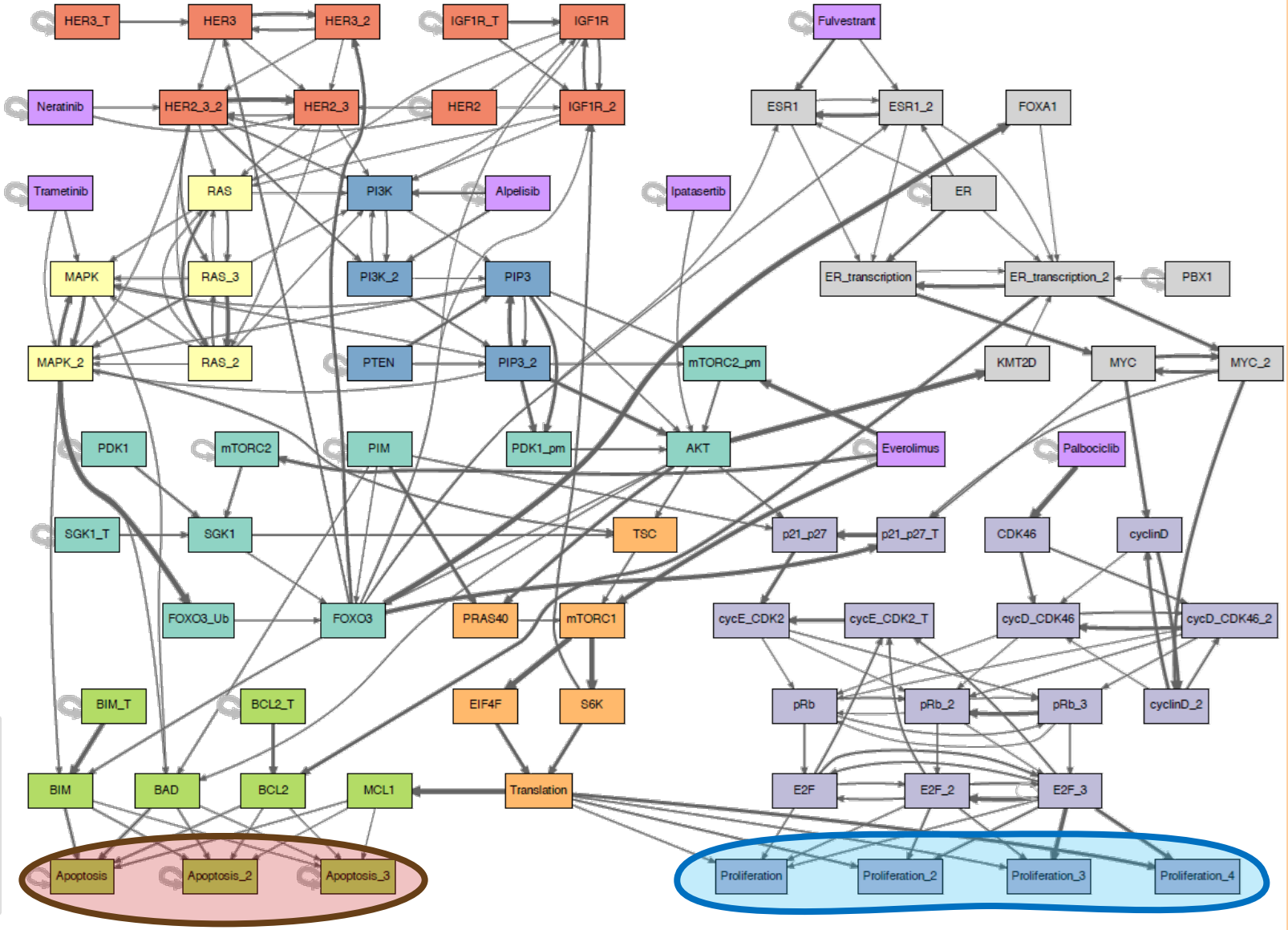

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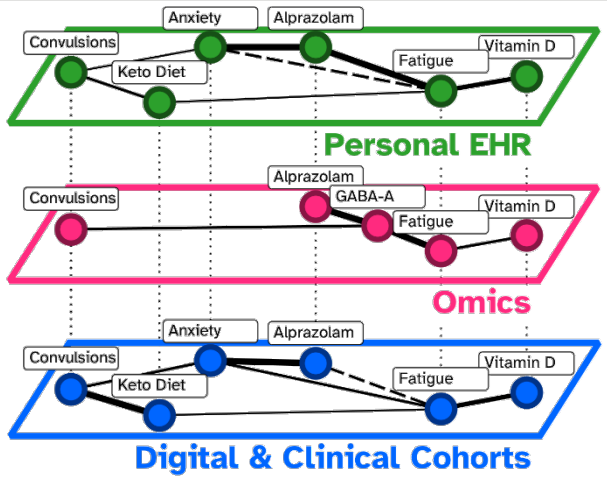

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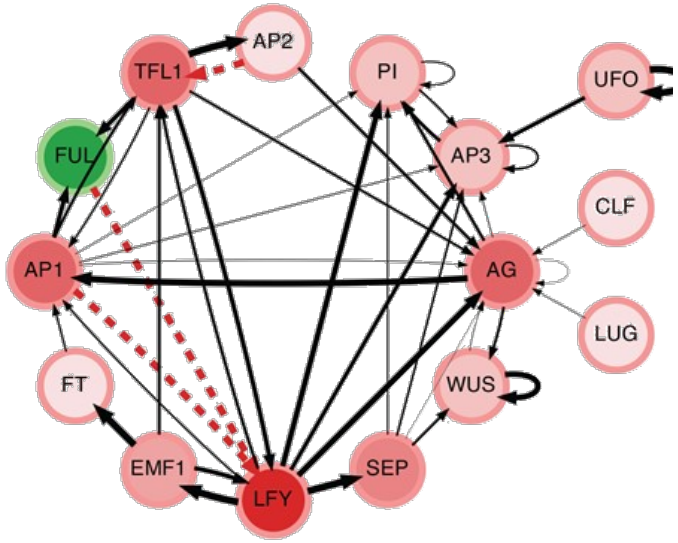

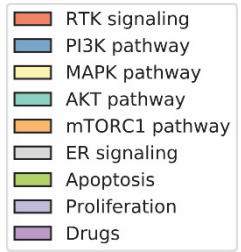

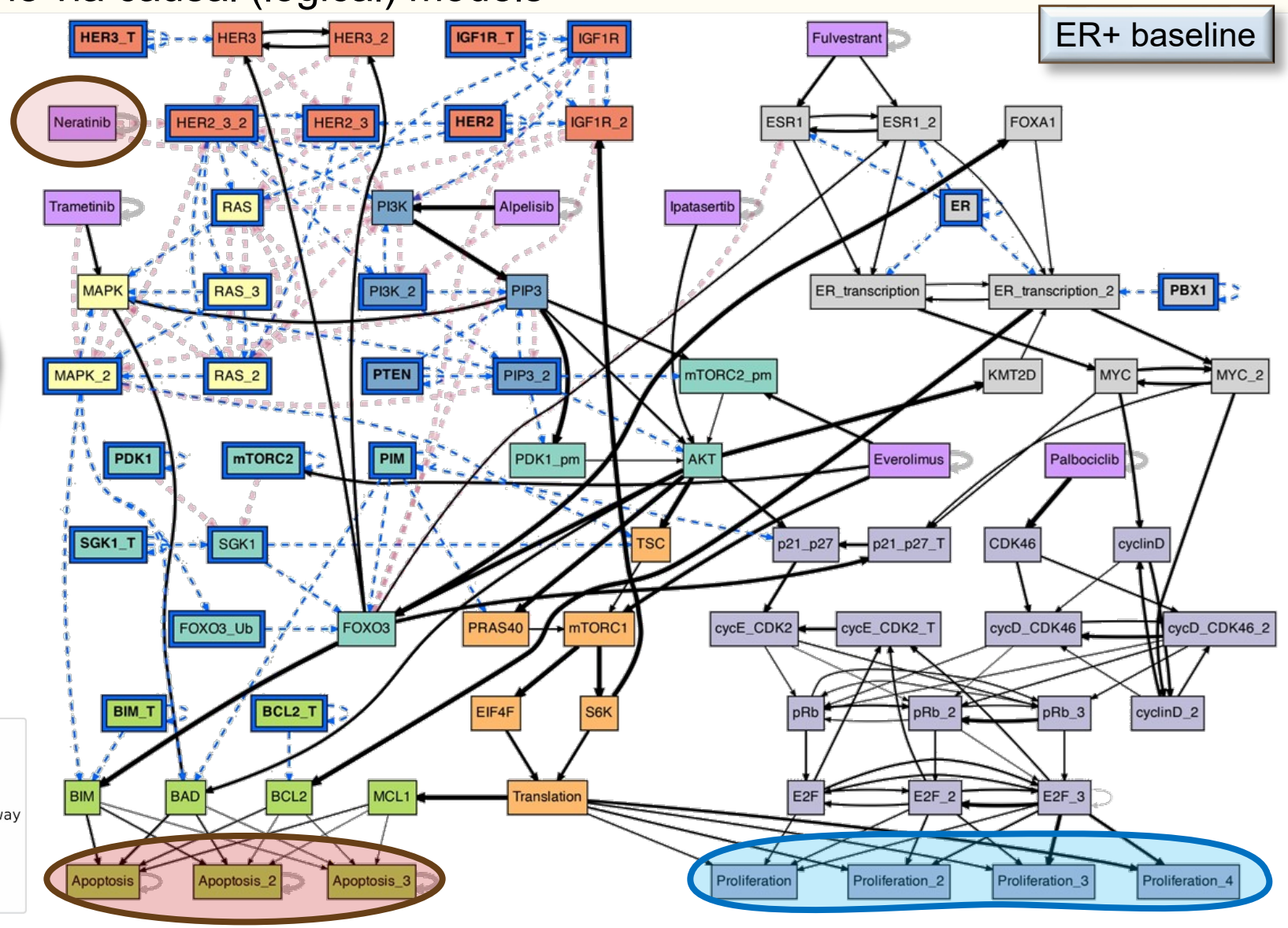

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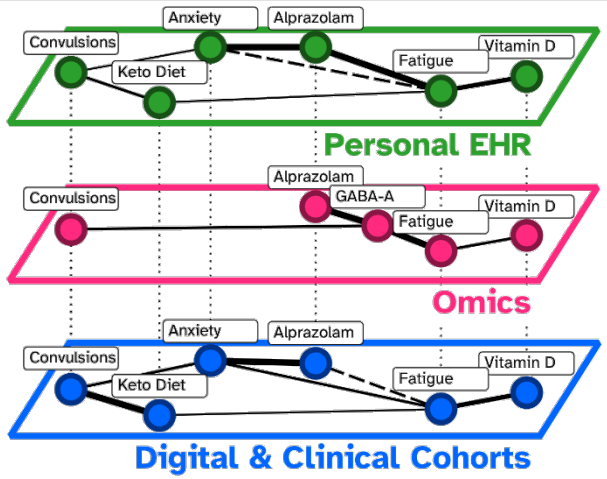

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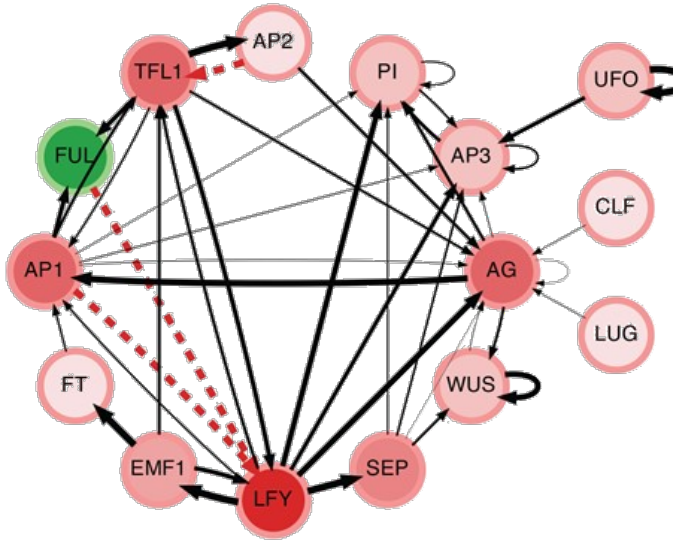

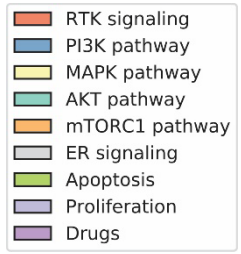

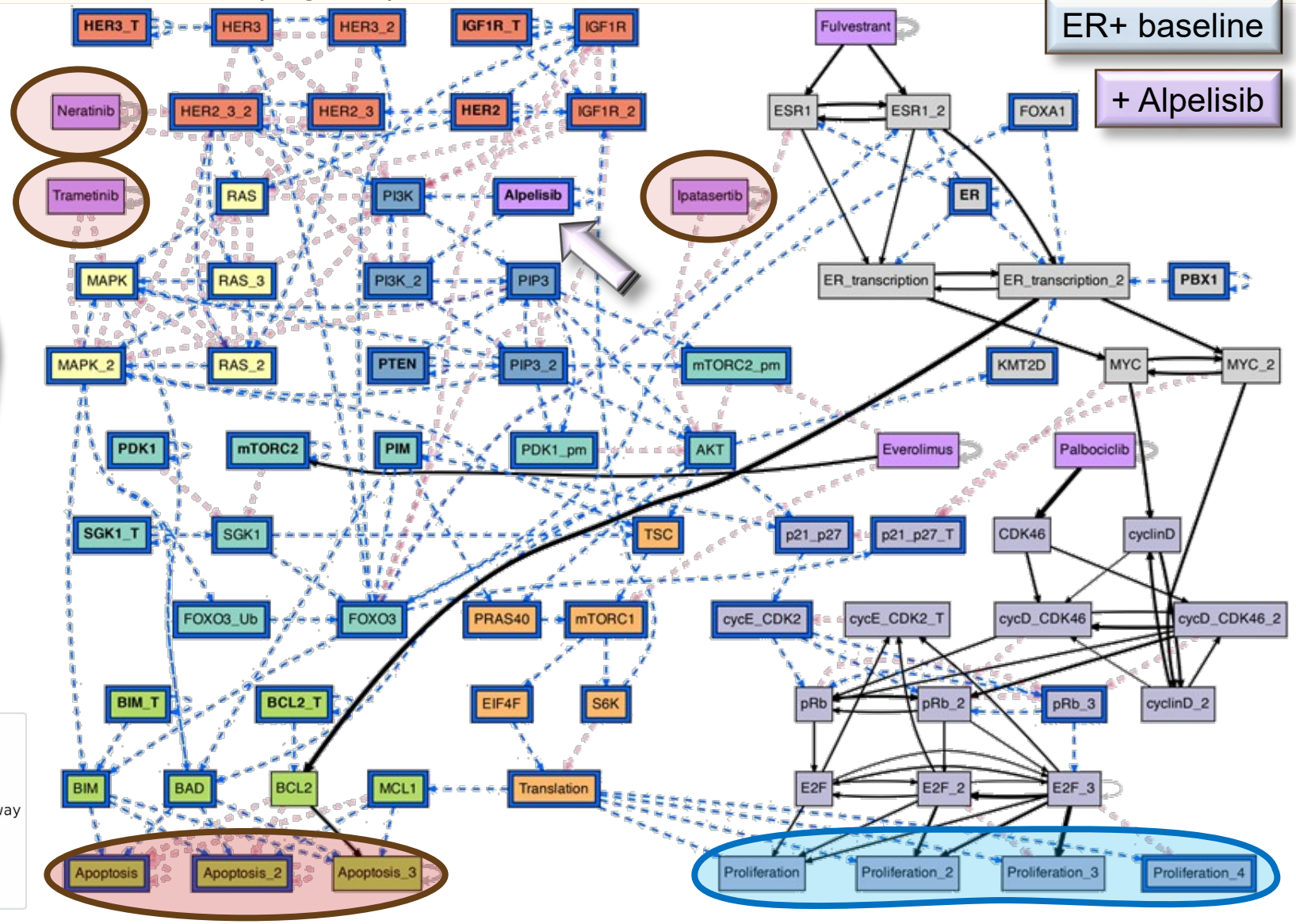

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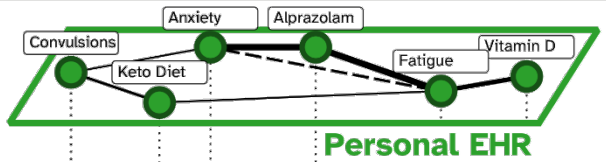

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Catalonia, Spain
Indiana, USA
AllOfUs (USA)
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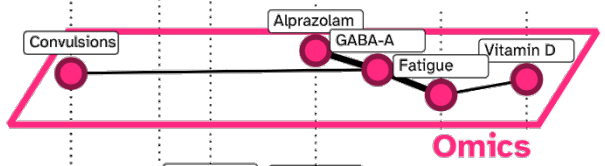
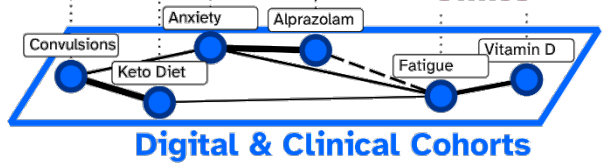


DisGeNet
DiseaseMeth
DISBIOME
Human Metabolome
. . .



Reddit
EFA Forums
ClinicalTrials.gov
PubMed/MEDLINE
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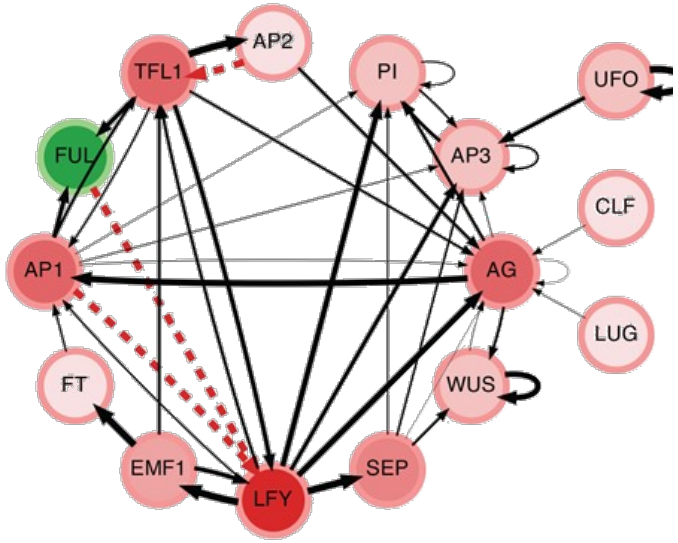

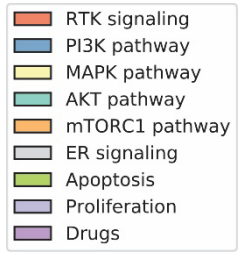

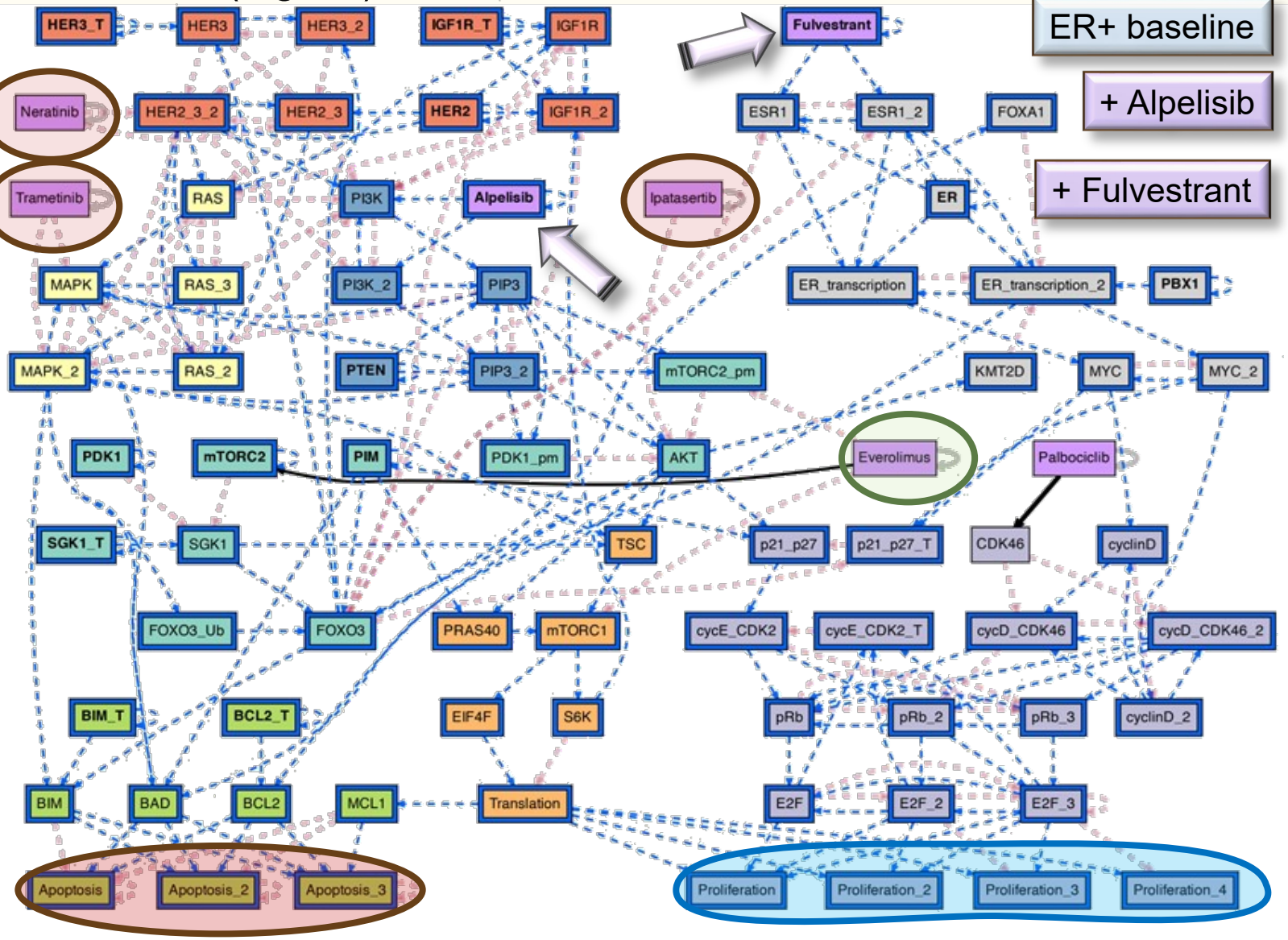

Parmer, Rocha & Radicchi [2022]. *Nature Communications*. **13**, 3457.
Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.

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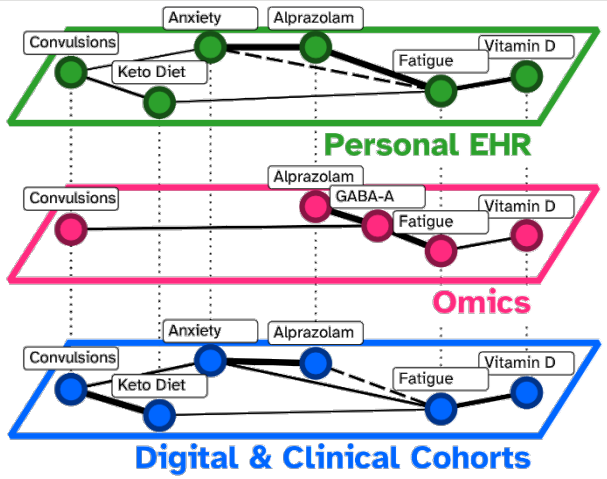
analyzing multilayer distance backbone via causal (logical) models



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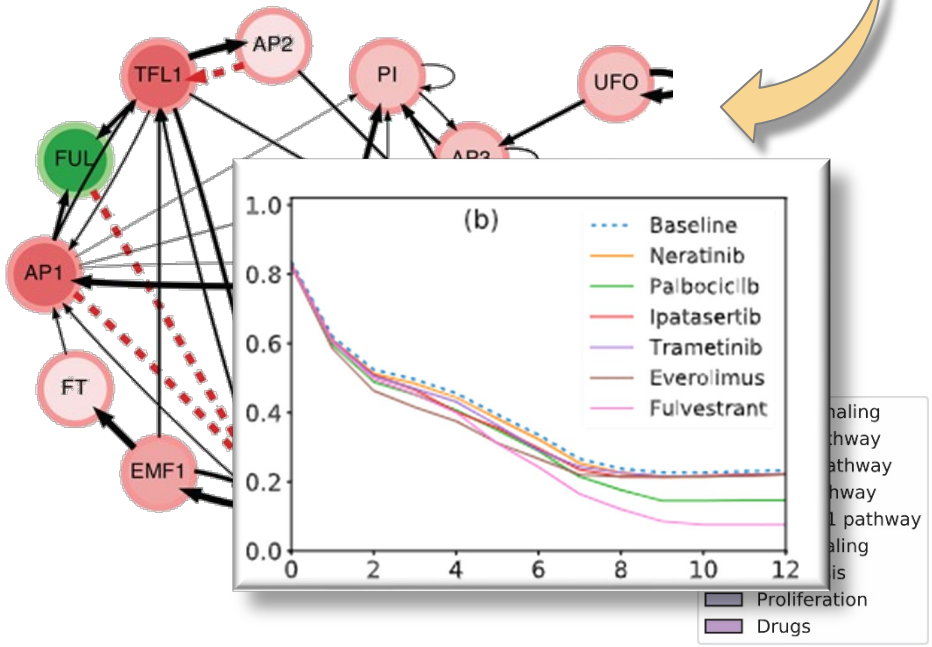

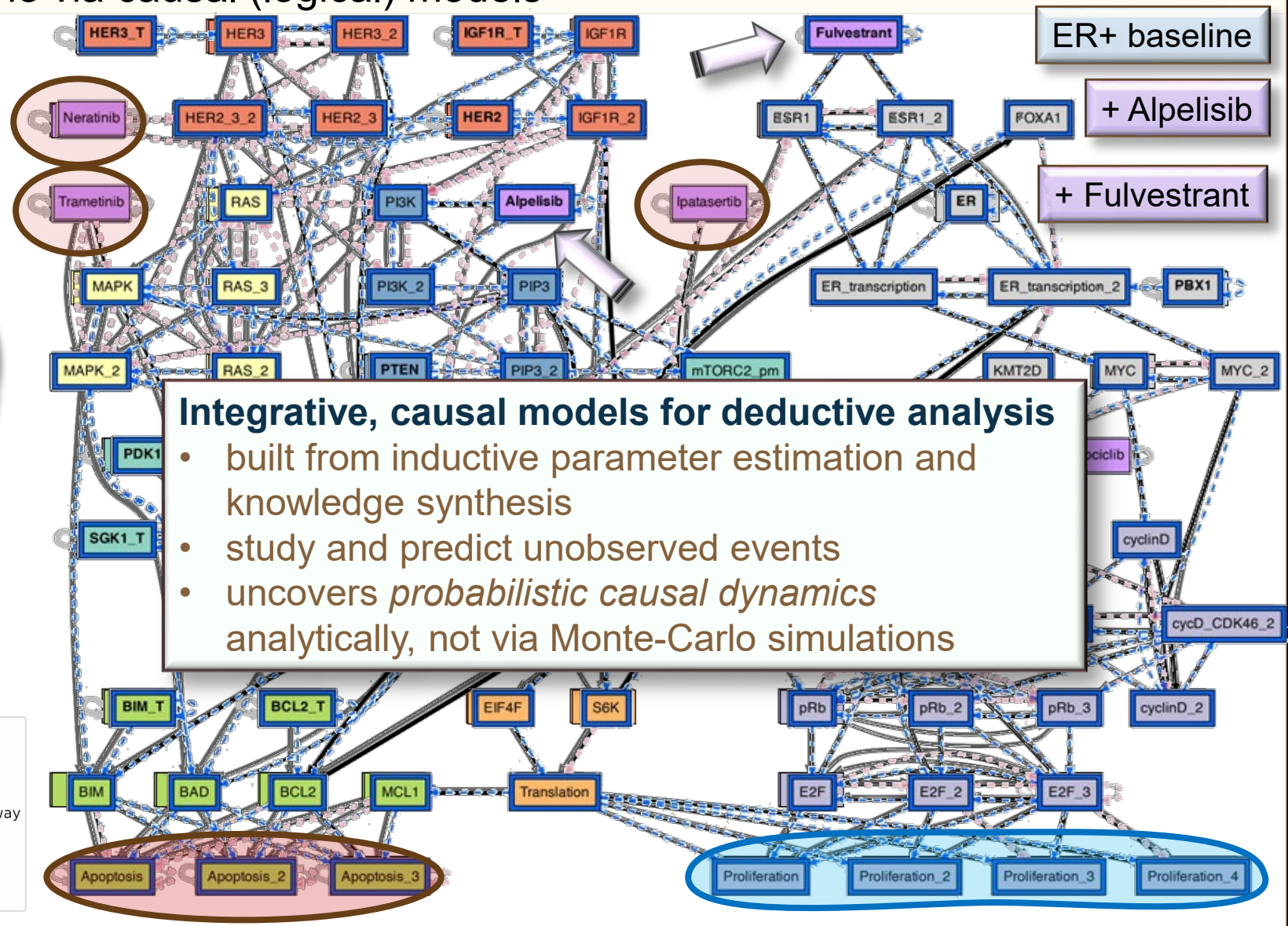

ER+ baseline

+ Alpelisib

+ Fulvestrant

Integrative, causal models for deductive analysis

- built from inductive parameter estimation and knowledge synthesis
- study and predict unobserved events
- uncovers *probabilistic causal dynamics* analytically, not via Monte-Carlo simulations

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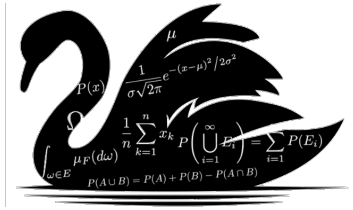
may work in complex interrelated domain (with rare control events)



unobserved scenarios

examples

Parameter estimation

Initial conditions

Simplified, Formal, explainable, actionable model/theory

Logical consequences

predictions

????

observations

Particular Instance

General Rule

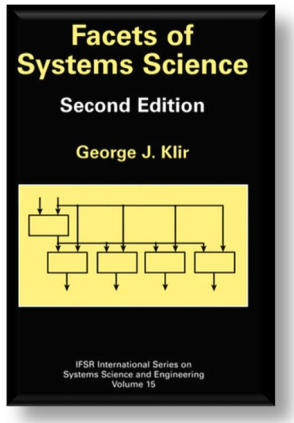
Symbols

Encoding

Measure

Measure

Measure



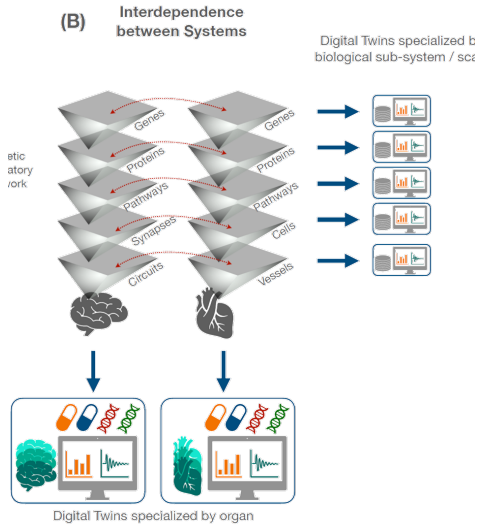
$World_0$

$World_1$

$World_2$

Howard Pattee

Robert Rosen



George Klir

Complex Physical Laws

Model and data simplification is key for feasibility and explainability.

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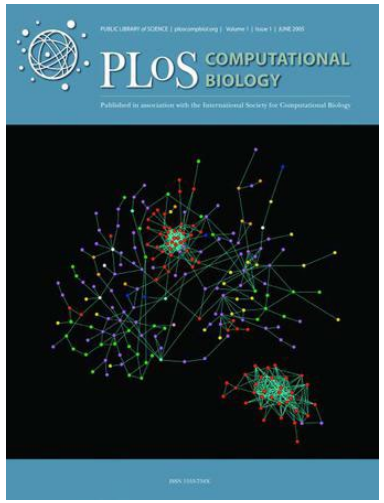
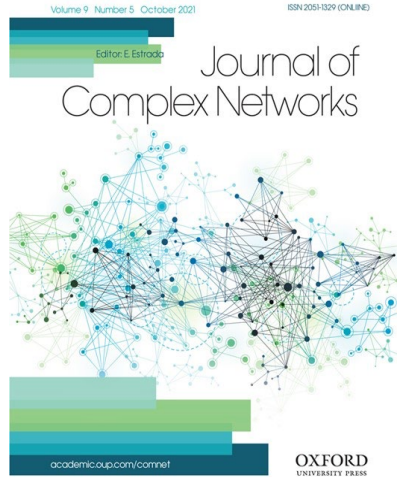
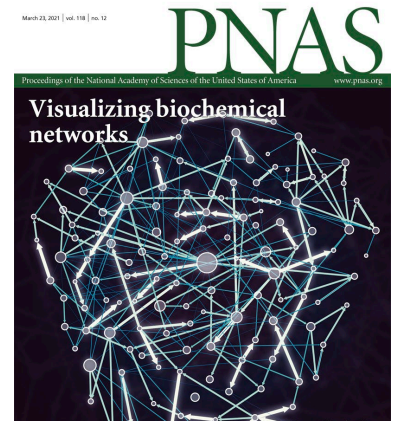
THANK YOU!
OBRIGADO!







github.com/CASCI-lab

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