Conductome

FROM THE PHYSIOLOME TO THE CONDUCTOME AND BACK: A Conceptual Framework

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Conductome

What is an "omic" perspective?

Related to the "totality" of something

Moleculome
Atomome
Particulome

Cause and effect?

"Micro"

Genome, epigenome, proteome, transcriptome, metabolome,…

Totality of structures, e.g., biological molecules – genes, proteins, metabolites

(Could have had a totality of functions)

Cause and effect?

"Macro"

Physiolome, infectome, microbiome, connectome, diseaseome,…

Totality of structures, e.g., organs/tissues, bacteria, virus, uni-cellular animals, neurons

(Could have had a totality of functions)

Cause and effect?

Ethome

Totality of behaviors

(Could have had a totality of structures)

Gomez-Marin, A., Paton, J. J., Kampff, A. R., Costa, R. M., and Mainen, Z. F. (2014). Big behavioral data: psychology, ethology and the foundations of neuroscience. Nat. Neurosci. 17, 1455–1462.

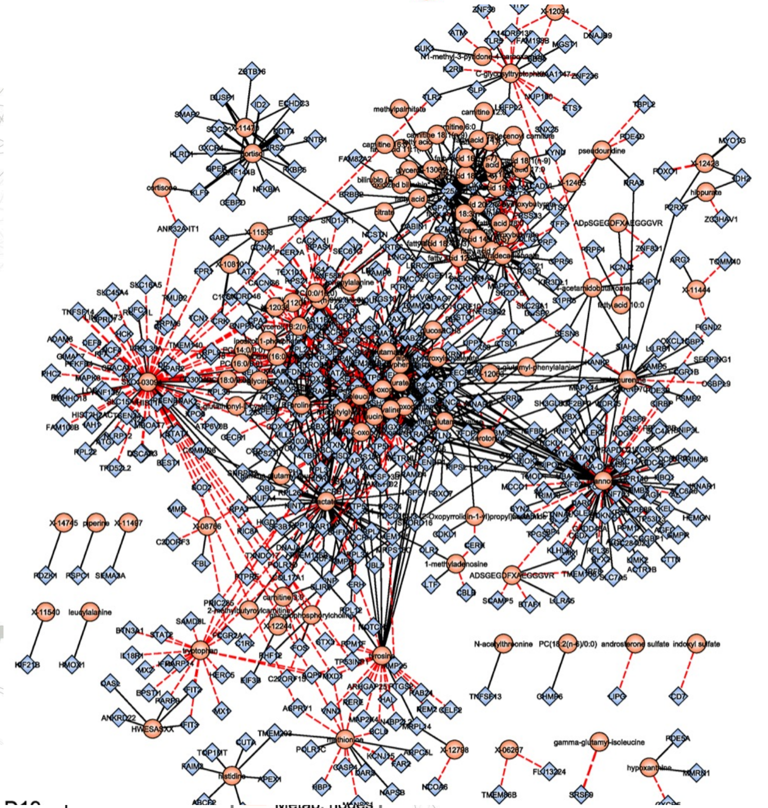
How do we represent “omes”

Representation 1: Networks (“Ecological communities”)

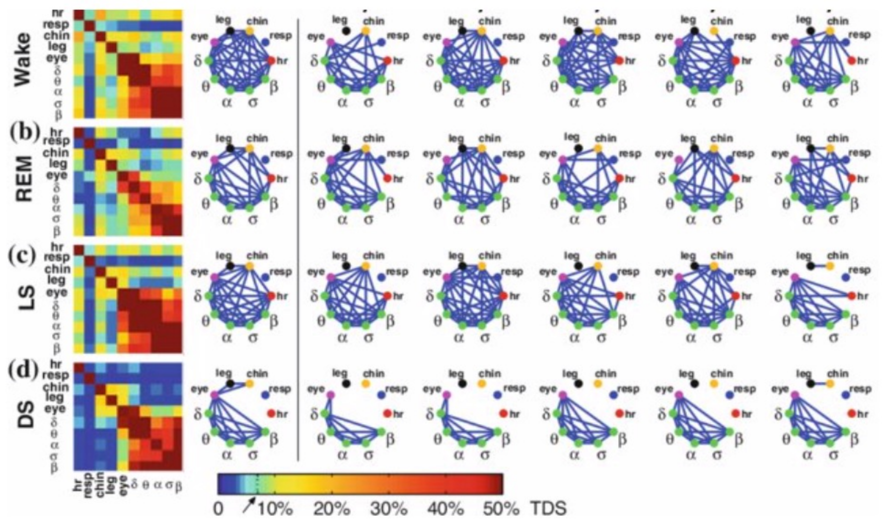
$$P(X_1, X_2,\ldots, X_i,\ldots, X_N) \rightarrow \{X_1, X_2,\ldots, X_i,\ldots, X_N, E(X_1, X_2), E(X_1, X_3),\ldots, E(X_i, X_j),\ldots, E(X_{N-1}, X_N)\}$$

$E(X_i, X_j)$ – measure of the relation - correlation

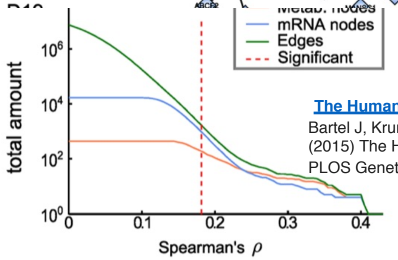
Multi-factoriality manifest in dimensionality N



- Nodes, X_i, can be structures, states, functions etc.
- Links can represent known relations/interactions or be inferential
- Both local and global information can be deduced
- Multi-factoriality manifest only at the global level
- What type of statistical ensemble is used – ”person” – longitudinal vs. transverse - or “place”?
- What scale of data (time and space) is used – 1 hour, 1 day, 1 month, 1 lifetime?



Ivanov and Bartsch, Network Physiology: Mapping Interactions Between Networks of Physiologic Networks, in Networks of Networks: the last Frontier of Complexity, Springer International, Editors: G. D''Agostino, A. Scala



The Human Blood Metabolome-Transcriptome Interface
Bartel J, Krumsiek J, Schramm K, Adamski J, Gieger C, et al. (2015) The Human Blood Metabolome-Transcriptome Interface. PLOS Genetics 11(6): e1005274.

How do we represent “omes”

Representation 2: (”Ecological”) Niches

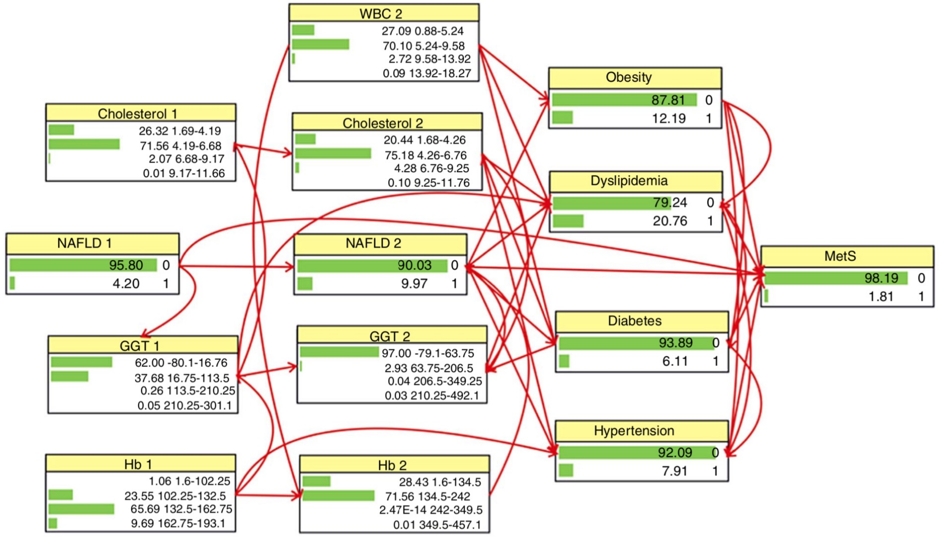
Bayesian networks are a link between the two representations

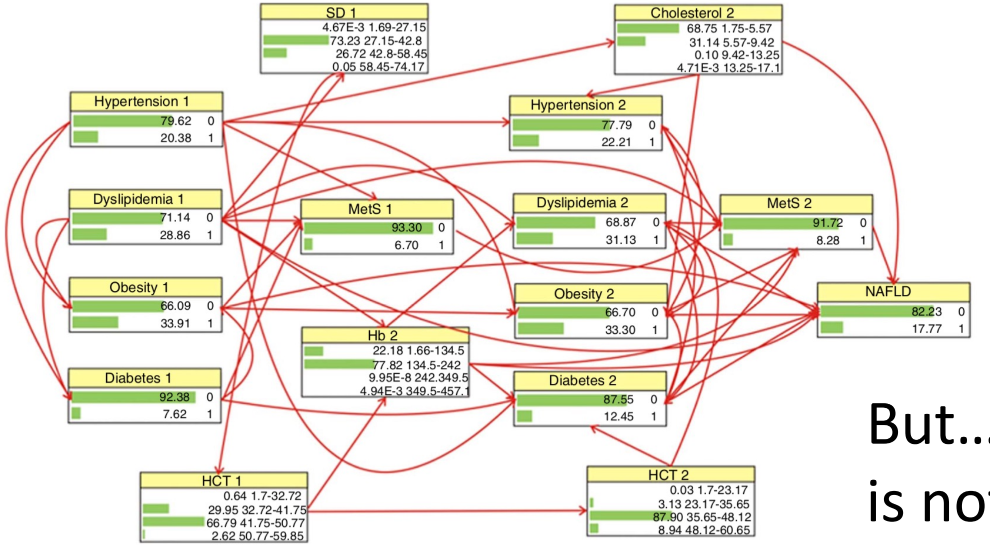
$$P(C|X_1,X_2,\ldots,X_N)$$

Multi-factoriality (multi-causality) manifest in dimensionality N

Calculated using:
Ensemble of “people”: Epidemiological perspective
Ensemble of “places”: Ecological perspective

C – can be a state, state change/event, place, function etc.





This is a ”physiolomic” perspective

But… your physiology is not a closed system

To what extent is NAFLD a “cause” of MS versus vice versa?

Zhang Y, Zhang T, Zhang C, et al. Identification of reciprocal causality between non-alcoholic fatty liver disease and metabolic syndrome by a simplified Bayesian network in a Chinese population. BMJ Open 2015;5:e008204.

Conductome

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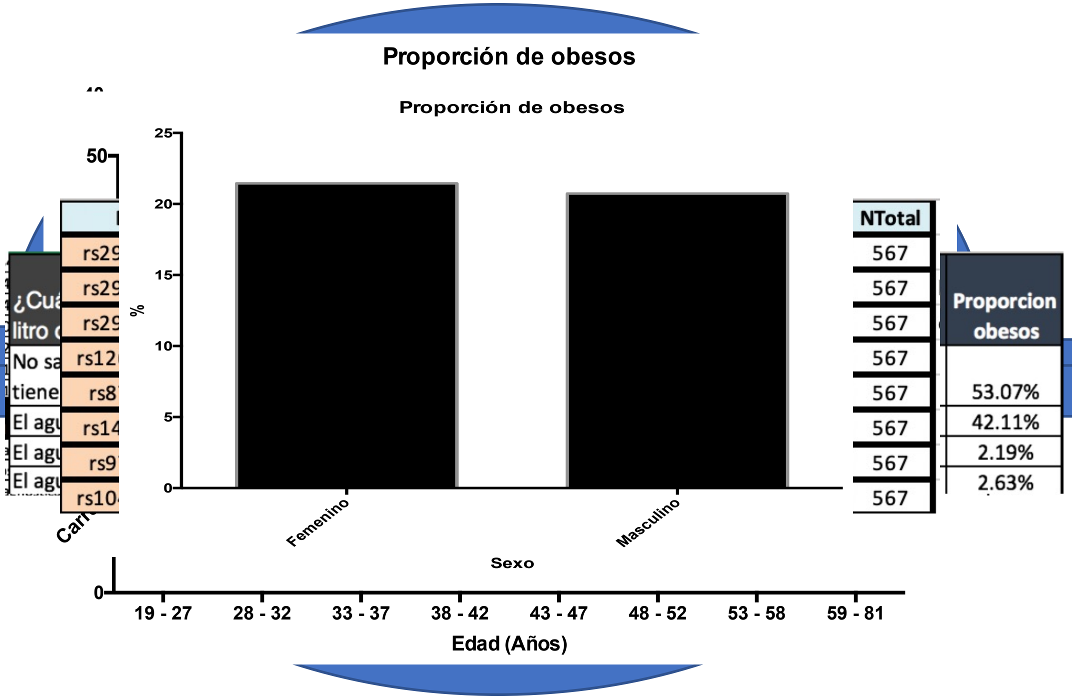
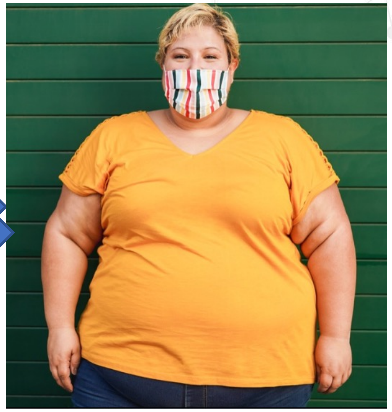
A Niche"omic" perspective of obesity (IMC > 30 kg/m²)

What is the obesity "niche"? What does the probability to be obese depend on?

Your age?
Your educational status?
Your gender?
Your genes?
Your height?
If you know how many calories are in a glass of water?

Some causes?





An effect

Project 42 data from 1076 academics, workers and students UNAM 2014 chilam.c3.unam.mx

Hypotheses

That human conduct/behavior can be ***predicted*** and ***explained*** (probabilistically)

a) Both transversally and longitudinally (though certain behaviors are more predictable and explainable than others)

b) With a Bayesian probability P(C |**X**), where C is the conduct/behavior of interest and **X** are the ”predictors/explainers” (though **X** is exceedingly ***multifactorial*** (multi-disciplinary) and dynamic – from genes to politics)

c) That there is an “internal” Conductome that is constructed by an organism, and which determines its behaviour; and an “external” Conductome that we will try to construct from data

d) With Machine Learning models being the most appropriate to construct P(C |**X**)

Caveats

We don’t have a good definition of what is a conduct/behavior
We don’t have a good taxonomy of behaviors
We don’t have data sets that cover the gamut of explainers (though we are trying - and making progress!)
We don’t have much idea about the myriad causal and non-causal relations between the **X**

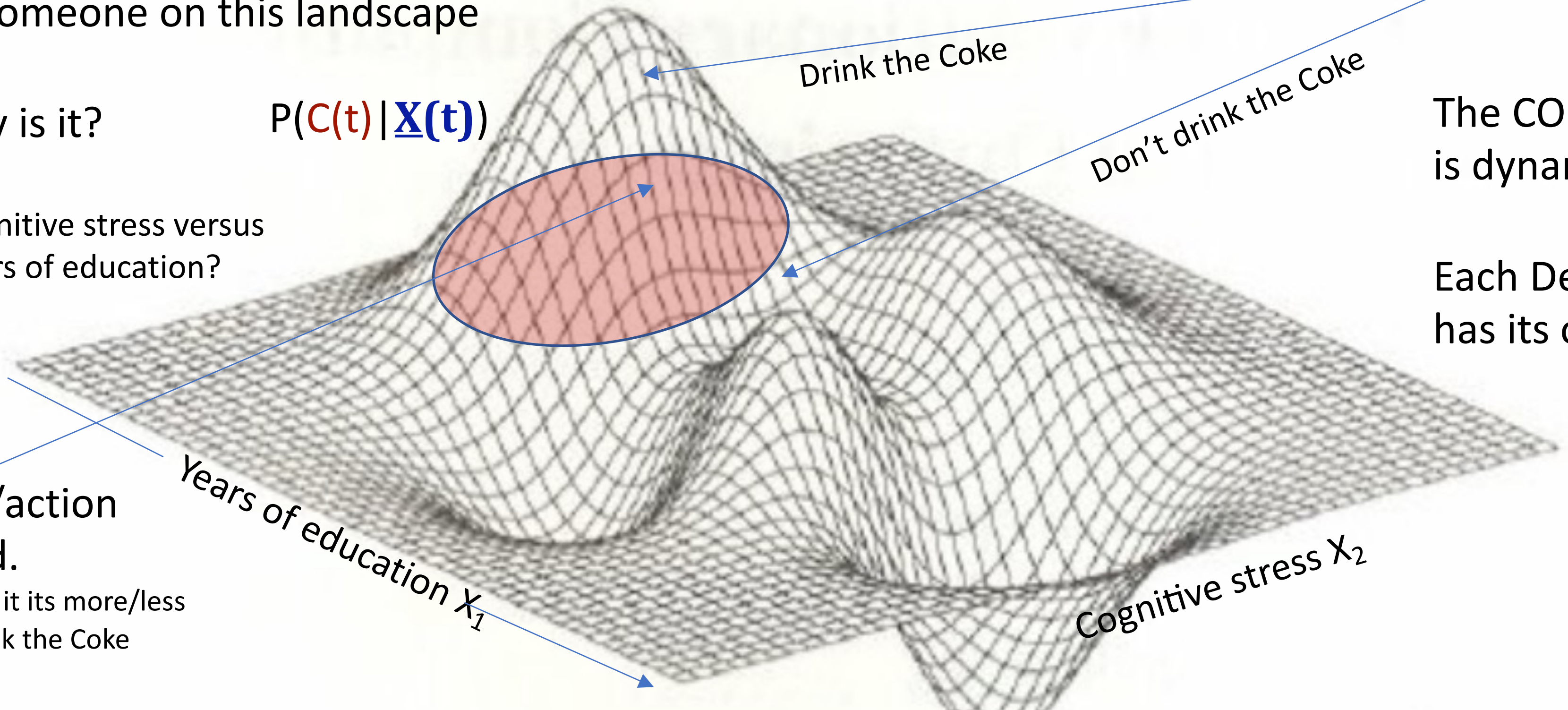
The CONDUCTOME Landscape

Conduct/behavior change means moving someone on this landscape

How do we move someone from here to here?

How easy is it? $P(C(t)|\underline{\mathbf{X}}(t))$

Reduce cognitive stress versus 5 more years of education?



The CONDUCTOME Landscape is dynamic and adaptive.

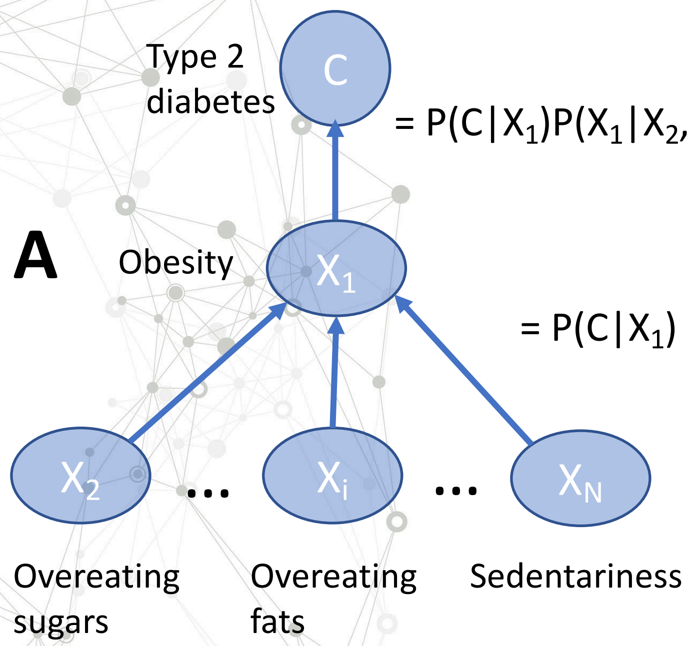
Each Decision/Action/Conduct has its own Landscape

Decision/action threshold.

Above/below it its more/less likely you drink the Coke

(X_1, X_2) – Two Conductome dimensions (among many) – represents the state of the person ("who" and "what" - old/young, happy/sad,…) and/or environment ("where" and "when" - at home/work, in Mexico/France,…)

The Challenge of Multi-factoriality/Multi-causality to an "omic" perspective – *The Problem of Calculation*



$$P(C,X_1,X_2,\dots,X_N)$$

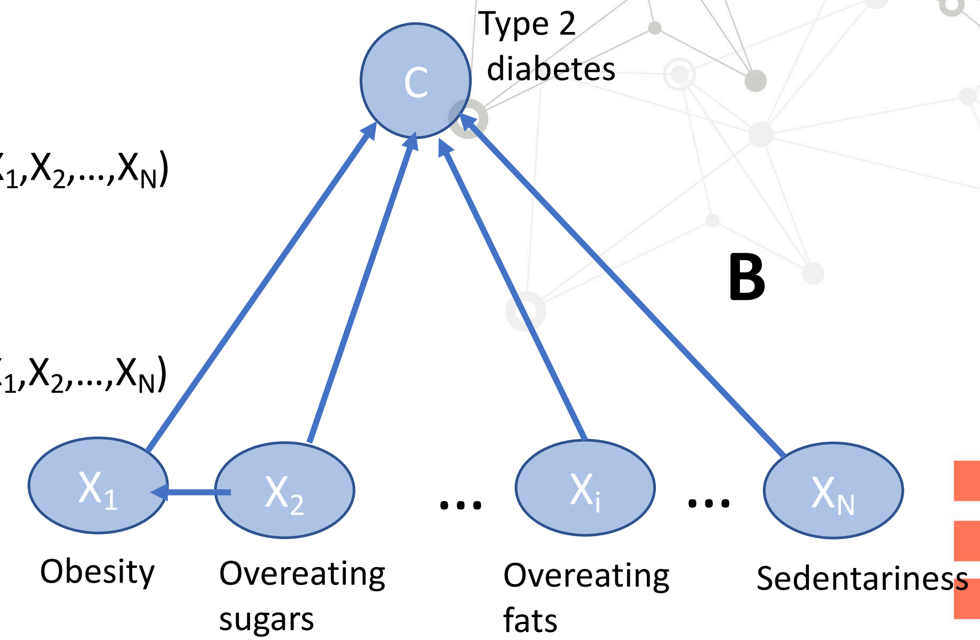
$$= P(C|X_1)P(X_1|X_2,\dots,X_N)$$

$$= P(C|X_1,X_2,\dots,X_N)P(X_1,X_2,\dots,X_N)$$

$$P(C|X_1,X_2,\dots,X_N)$$

$$= P(C|X_1)$$

$$= P(C,X_1,X_2,\dots,X_N)/P(X_1,X_2,\dots,X_N)$$



Multi-factorial probabilities cannot be calculated in a frequentist sense

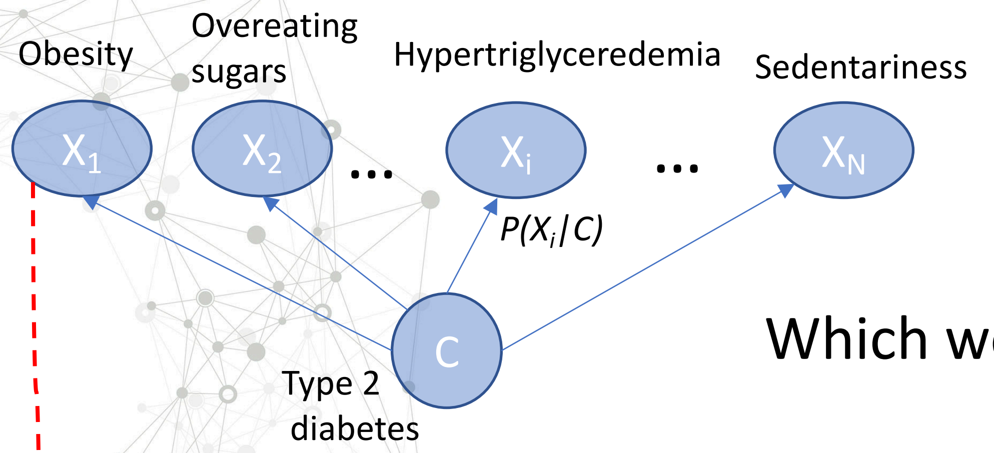
Bayes Theorem

$$P(C|X_1,X_2,\ldots,X_N) = P(X_1,X_2,\ldots,X_N \mid C)\, P(C) / P(X_1,X_2,\ldots,X_N)$$

Assuming that the X_i are independent

$$P(X_1,X_2,\ldots,X_N \mid C) = \prod_{i=1}^{N} P(X_i|C)$$

Which we can represent as a network…



Obesity type I, II or III
Obese for one year versus 30
Obesity began at age 5 or 65?
…

This network involves variables that could be considered part of the ***Physiolome*** – Type 2 diabetes, hypertriglyceredemia and obesity, as well as variables that can be considered as conducts – overeating sugars and sedentariness

An Example (EXTERNAL) Conductome

Behaviour C = No exercise on weekdays

Question	Answer	Number of people with X	Number of people who do not exercise and X	Number in population	Number not exercising on weekdays	% who do not exercise	% who do not exercise and X	Predictive model weight (score)	Statistical reliability (Epsilon)	Cause or consequence
What chores do you do? Childcare	Yes	41	29	292	120	41.10%	70.73%	0.38	3.86	Cause
How regular is your bedtime schedule?	1 - 2 hrs	17	14	292	120	41.10%	82.35%	0.67	3.46	Both
Do you exercise on the weekend?	No	182	97	292	120	41.10%	53.30%	0.06	3.35	Both
What time do you go home from work?	15:00	32	22	292	120	41.10%	68.75%	0.34	3.18	Cause
How many hours do you sleep on weekdays?	4-5 hours	65	39	292	120	41.10%	60.00%	0.18	3.1	Consequence
Approximately how many free hours do you have a day on weekdays?: I don't know	Yes	24	17	292	120	41.10%	70.83%	0.39	2.96	Cause
Where do you eat during the week?: Position 2	In street stalls	9	8	292	120	41.10%	88.89%	0.9	2.91	Both
What chores do you do?: Wash the bathroom	Yes	172	89	292	120	41.10%	51.74%	0.03	2.84	Cause
What chores do you do?: Shake	Yes	158	82	292	120	41.10%	51.90%	0.03	2.76	Cause
What type of vehicle is transported from home to work? and How long does each one last approximately IN MINUTES?: Metro: Value	60 min	11	9	292	120	41.10%	81.82%	0.65	2.75	Cause
How do you get your snacks?: I buy it at a stall	Yes	50	30	292	120	41.10%	60.00%	0.18	2.72	Both
What chores do you do on the weekend?: Childcare	Yes	60	35	292	120	41.10%	58.33%	0.15	2.71	Cause
Where do you have breakfast? Select in order of frequency: Position 1	In the kitchen at work	27	18	292	120	41.10%	66.67%	0.3	2.7	Both

These are just the most statistically significant predictors from a small subset of the predictors/explainers, **X**.

> 1.96 ~ 95% confidence interval

Applications to obesity and metabolic disease

Population of 292 academic and non-academic workers of the UNAM in 2019.

Some predictors/explainers are other conducts, where some are more "voluntary" than others; some are environmental factors; some are more "actionable" than others

Another Example (EXTERNAL) Conductome

Conductome

Behaviour C = Exercise > 2.5 hours weekly

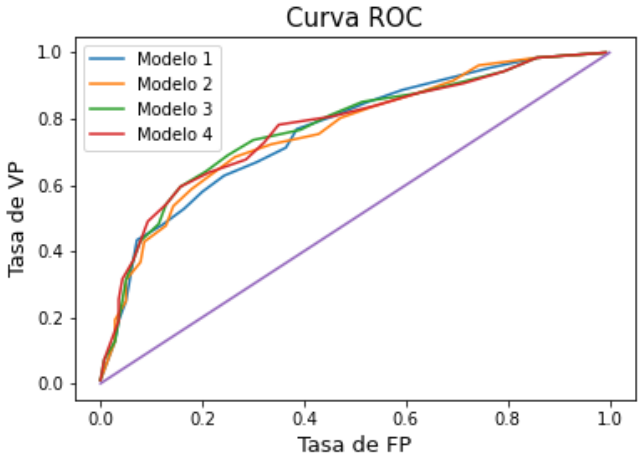
	item	answer given	N	Nc	Nc/N	Nx	Nxc	Ncx/Nx	Epsilon	Score
1	How do you consider your physical condition?	Good	530	278	0.52	173	142	0.82	7.80	1.52
2	Do you exercised regularly?	Yes	517	278	0.54	390	278	0.71	6.94	0.91
3	How do you consider your health ?	Very good	528	277	0.52	75	62	0.83	5.24	1.56
4	How do you consider your physical conditin?	Very good	530	278	0.52	52	46	0.88	5.20	2.04
5	Three_Factor_Eating_Questionaire: On a scale of 1 to 8, where 1 means “not restrict my eating” (eat what I want, wherever I want) and 8 means “restrict my eating” (constantly limit myself and never eat it): Which number would best describe you?	´7-8	297	151	0.51	33	31	0.94	4.95	2.74
6	Locus_of_control_exercise: My lack of initiative prevents me from exercising	Dos not describe me at all	215	103	0.48	53	43	0.81	4.84	1.46
7	Locus_of_control_exercise: My lack of will prevents me from exercising	Dos not describe me at all	215	103	0.48	47	38	0.81	4.52	1.44
8	Locus_of_control_exercise: Although I try, I never manage to exercise	Dos not describe me at all	215	103	0.48	83	60	0.72	4.45	0.96
9	Locus_of_control_exercise: After I finish my activities I don't have time to exercise	Dos not describe me at all	215	103	0.48	34	29	0.85	4.36	1.76
10	How much do you think you eat ?	Recomended amount	521	277	0.53	252	168	0.67	4.29	0.69
11	Self-efficacy_exercise: Sticking to an exercise routine. How confident are you that you can stick to your routine despite these situations? Without the support of family or friends.	´9-10	215	103	0.48	70	51	0.73	4.18	0.99
12	Gratification_delay_frequency_responses: Select the response that most characterizes you. I have always tried to eat healthy because it is a good decision for the future	Always	297	151	0.51	61	47	0.77	4.09	1.21
13	Locus_of_control_exercise:My lack of organization prevents me from exercising	Dos not describe me at all	215	103	0.48	43	34	0.79	4.09	1.33
14	Locus_of_control_exercise: My inconstancy prevents me from exercising	Dos not describe me at all	215	103	0.48	45	35	0.78	4.01	1.25
15	Locus_of_control_exercise: My homework prevents me from exercising	Dos not describe me at all	215	103	0.48	31	26	0.84	4.01	1.65
16	Do you or any member of this household have: Cleaning services?	Yes	521	278	0.53	165	113	0.68	3.89	0.78
17	Do you eat healthy ?	Yes	521	277	0.53	375	236	0.63	3.79	0.53
18	Locus_of_control_exercise: My responsibilities prevent me from exercising	Dos not describe me at all	215	103	0.48	32	26	0.81	3.78	1.47
19	Self-efficacy_exercise: Sticking to an exercise routine. How confident are you that you can stick to your routine despite these situations? After recovering from an illness that prevented you from continuing to exercise.	´9-10	215	103	0.48	48	36	0.75	3.76	1.10

Applications to obesity and metabolic disease

Population of 636 undergraduate students from various Mexican universities in 2022

Over 1000 questions in multiple questionnaire that cover a large gamut of areas and disciplines:

Negative emotions (EN), such as stress, anxiety and depression; Delay of gratification (RG); ThreeFactorEatingQuestionaire; Locus of control - food control (LCA); Locus of control exercise (LCE); Exercise attitudes and beliefs (EC); Obesity attitudes and beliefs (CO): What students believe regarding obesity; Self-efficacy food (AA); Self-efficacy exercise (AE); Motivation (M) for weight control; Food (A) : Options that most help the student to take care of their weight with respect to food. University (Uni.): Section where your condition, stress, health, etc. during the both before and after COVID-19 are indicated; Diseases (Enf.) : Diseases that the student suffers or has suffered; Figure (F): What the student thinks about their body; Obesity (O): Section where the student is asked if he has been diagnosed with obesity; Belongings (P): Objects or services that the student possesses; Work (T): Questions about the student's work. Habits (V): Section on habits of the student; Housing (Viv.) : Questions about the student's housing.



Highly predictive classifier models can be deduced. These models are ***highly multi-factorial***. More than 20% of the total number of features are predictive at the 95% confidence interval.

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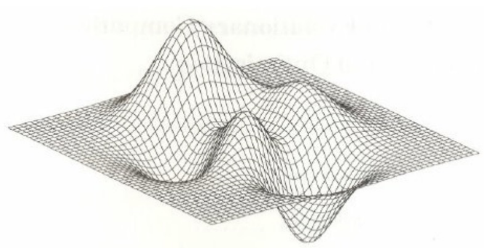
The action can change your physiological state.

E.g., elevation in ghrelin → foraging behaviour

These CONDUCTOMEs represent

$$P(A_k \mid \mathbf{S}(\{s_{Ii}(t)\}), \mathbf{O}(\{o_{Ii}(t)\}), \mathbf{E}(\{e_i(t)\}))$$

Probability for a subject S in a state $(\{s_{Ii}(t)\})$ and in an environment $\mathbf{E}(\{e_i(t)\})$ to take an action A_k (potentially involving an object $\mathbf{O}(\{o_{Ii}(t)\})$).



We are using an ***external*** ensemble

This is a behavioural approach. We get BIG, DEEP data and we correlate observed actions with subject, object and environment state variables.

It doesn't give us the WHYs though! Or, at least only very indirectly.

A true understanding of the WHYs requires a better understanding of the ***internal*** ensemble.

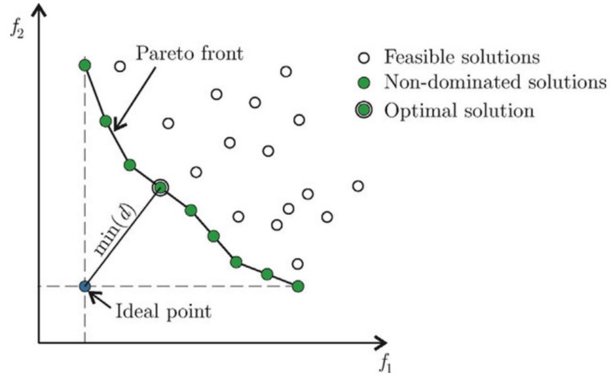
WHY does someone take the escalator versus the stairs?

When is a decision “good” versus “bad”?

We need a metric to measure it.
Rational decision making implies that there is a unique utility function that we optimize

What is the utility function here?

DT = the time difference between taking the stairs and taking the elevator?
DE = the difference in physical energy expended in one route versus another?
DH = the relative perceived health benefit of one versus the other (think how this can change pre-COVID versus post-COVID!)?
DS = the socialization benefit in the case you would take one versus the other with coworkers?
Others?



How do we balance these tradeoffs and make our decision?

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How do we make decisions?

For a potential utility we assign a value function v_i
For N_v value functions we have: $\mathbf{V} = (v_1, v_2, \ldots, v_{Nv})$
Every action A_k leads to a change: $D\mathbf{V}(A_k) = (Dv_1(A_k), Dv_2(A_k), \ldots, Dv_{Nv}(A_k))$

A decision is "good" versus "bad" with respect to a given value function v_i if $Dv_i(A_k) > 0$ ("good" decision) versus $Dv_i(A_k) < 0$ ("bad" decision).

It is not possible to have $Dv_i(A_k) > 0$ for all v_i. E.g., in the stairs-elevator situation if the elevator was slow where $DT(\textit{stairs versus elevator}) > 0$ but $DE(\textit{stairs versus elevator}) < 0$. "You can't have your cake and eat it".

$D\mathbf{V}(A_k)$ can take different values depending on where the measurement is made – pre-action versus post-action.

Post-action, $D\mathbf{V}(A_k)$ represents the real or perceived payoffs of the action, i.e., they are outcomes.

For a pre-action evaluation $<Dv_i(A_k)>$ represents the predicted value change due to the action. Although $<\ldots>$ could in some circumstances be calculated objectively, in general it comes from an ***internal*** prediction model for estimating what the change in value will be.

The action can change your physiological state

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$$P(A_k \mid \langle D\mathbf{V}(A_k)\rangle) = P(A_k \mid \langle Dv_1(A_k)\rangle, \langle Dv_2(A_k)\rangle, \ldots, \langle Dv_{Nv}(A_k)\rangle)$$

The probability to take the action A_k is conditioned by the predicted payoffs from the action along a set of value functions.

To evaluate the probability of the action then the person needs a prediction model for each value function

$$P(Dv_i(A_k) \mid \mathbf{S}(\{s_{Ii}(t)\}, \{e_i(t)\}), \mathbf{O}(\{o_{Ii}(t)\}, \{e_i(t)\})$$

In other words, we predict what the probability is for a change in the value function v_i given the subject, object and environment states. Thus, for example, in the stairs-elevator example – if the subject is in a "very tired" state, then the probability for a large perceived increase in effort, DE, to take the stairs would be higher than in the "non-tired" state, with the consequence that the probability function will be such that $P(\textit{take the stairs} \mid \langle DE(\textit{take the stairs})\rangle_1) < P(\textit{take the stairs} \mid \langle DE(\textit{take the stairs})\rangle_0)$, where $\langle DE(\textit{take the stairs})\rangle_1$ is the predicted effort for taking the stairs given that the subject is in the state 1 = "very tired" and $\langle DE(\textit{take the stairs})\rangle_0$ is the predicted effort for taking the stairs given that the subject is in the state 0 = "not tired".

The predicted change in v_i we then take to be

$$\langle Dv_i(A_k)\rangle = F(P(Dv_i(A_k) \mid \mathbf{S}(\{s_{Ii}(t)\}, \{e_i(t)\}), \mathbf{O}(\{o_{Ii}(t)\}, \{e_i(t)\}))$$

Your physiological state affects this calculation.
e.g., are you very tired or not

for a given function F( ) that maps the probability function for the value function changes conditioned on the subject, object and environment states into an "expected" change.

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Conclusions

1. "Omic" perspectives are ambitious, challenging and data "hungry"
2. Some are easier to characterize than others – structures, functions, interactions,…
3. "Networks" are a useful representation, subject to the caveats of 2. and the requirements of 1.
4. An ecological perspective offers two network characterizations – "communities" and "niches" that can also have a natural Bayesian interpretation
5. The Physiolome can be represented by either characterization but… it is not a closed system!
6. In many important applications it is "Conduct" that is the prime driver in changes in physiologic state (e.g., obesity and metabolic disease)
7. The importance of conduct and an "omic" point of view leads us to consider the CONDUCTOME using a niche perspective - P(conduct | everything)
8. A phenomenological model of the Conductome (partial) can be constructed empirically
9. Conduct is the output of a metamodel whose inputs are the expected payoffs for a set of objective functions that are "computed" from internal predictive models for each payoff function

Wednesday: How physiology is driven by conduct and vice versa in the context of metabolic disease

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