From Evolution to Daily Life: The Importance of Timescale in Network Physiology

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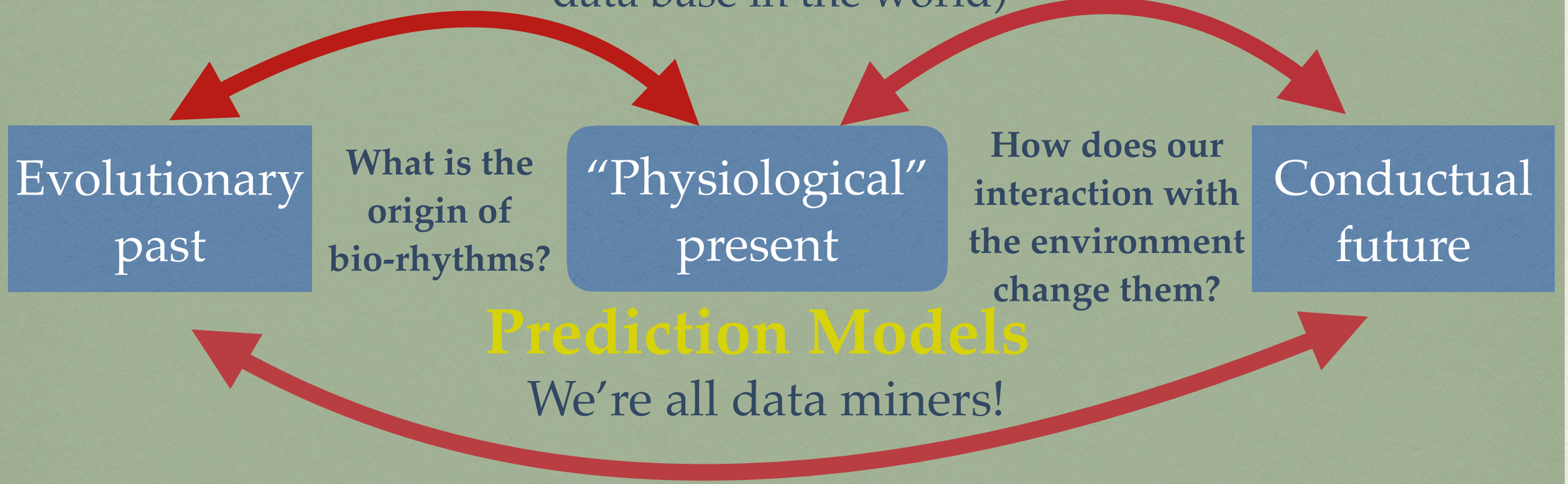
Matrix Institute Symposium: Mathematics of Physiological Rhythms
9-13th September 2019

Project 42

(getting the "deepest" data base in the world)

Multiple data types: time series, metric, categorical,…



Conductome

(the totality of factors that affect human behaviour)

Project 42

Getting the "deepest" database in the world

Phase 0: ENSANUT 2006, 2012; ENCOPREVENIMSS (National health surveys)

Phase I: (03-05/2014) 1,076 academics and non-academics from 12 institutes and faculties at the UNAM

2,524 variables - Genetics, epidemiolgical, physiological (blood work), anthropometric… **Epidemiological**: Personal (81), Personal histories (130), Family historias (548), Self-evaluation of health (226), Nutrition (220), Life style (390), Health knowledge (293)

Phase II: (03/2017-09/2018) 700 medical students of the Fac. Med UNAM; (06/17) 100 academics y non-academicos from the FM. Addition of psychological variables (locus of control, self-esteem,…).

Phase III: (12/2018-02/2019) 100 type 2 diabetics from the ISSTE

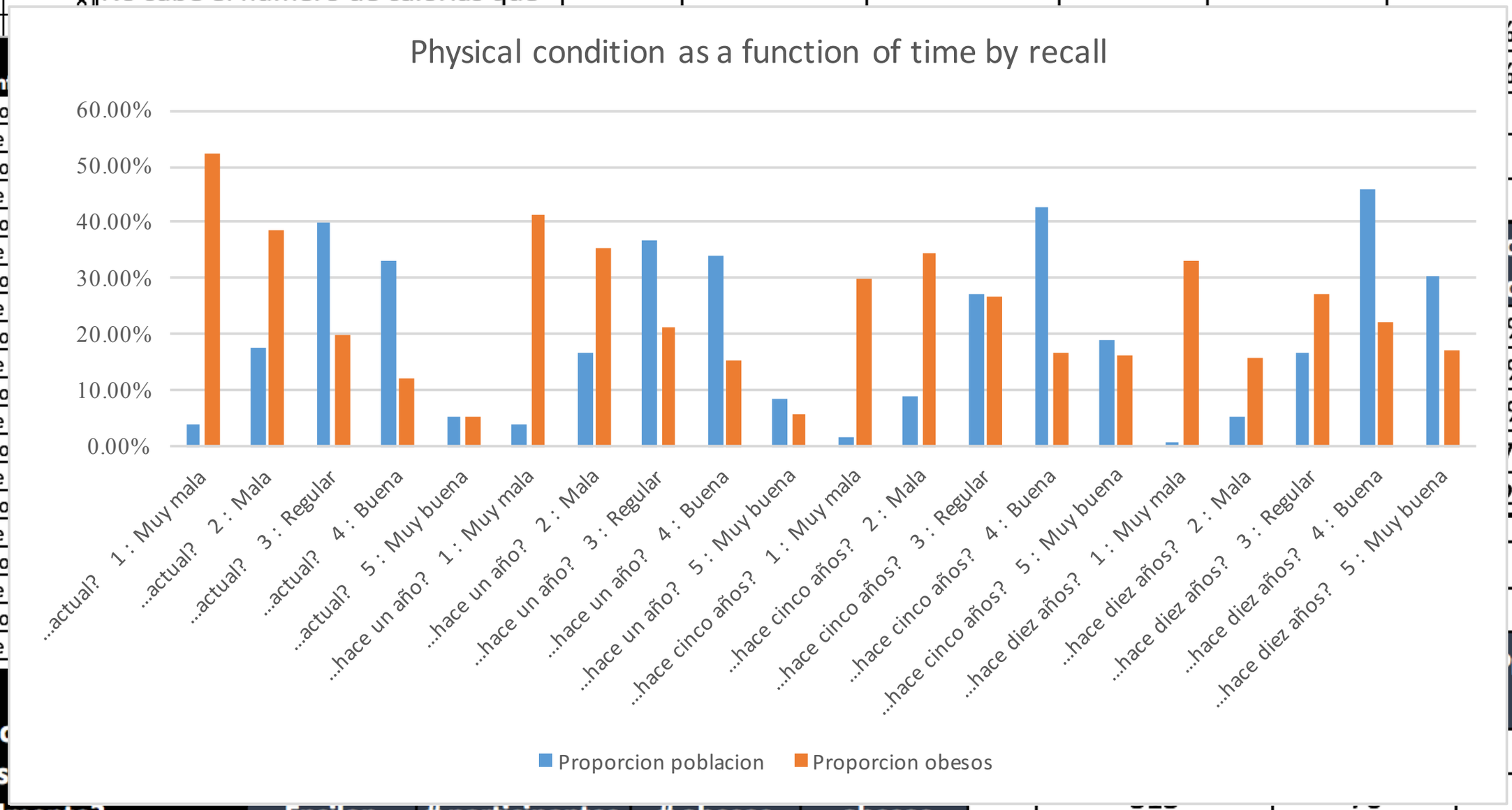
Phase IV: (06-09/2019) Follow up on the 1,076 from Phase I and 500 new participants. Repetition of laboratory analysis. Detailed "What did you do today?" questionaire. Construction of a machine-learning based analysis platform and publication of all data.

Phase V: (01/19-12/19) Construction and publication of data base associated with Phases 1-4 with a Machine learning based analysis platform

Phase VI: (9/19-12/19) fMRI, EEG, ECG, actigraphy, other physiological measurements, MCII

Variable	Valor	Epsilon	Nx	Nxc	N	Nc	Pc	Pxc	Descripción
Aestatura	1	4.801461	91	38	1076	228	0.2119	0.4176	Estatura que estima tener el encuestado < 1.5 : 1
Aestatura	2	-0.92449	399	77	1076	228	0.2119	0.193	Estatura que estima tener el encuestado [1.5, 1.6) : 2
Aestatura	3	-1.09413	366	69	1076	228	0.2119	0.1885	Estatura que estima tener el encuestado [1.6, 1.7) : 3
Aestatura	4	0.143796	185	40	1076	228	0.2119	0.2162	Estatura que estima tener el encuestado [1.7, 1.8) : 4
Aestatura	5	-1.63546	32	3	1076	228	0.2119	0.0938	Estatura que estima tener el encuestado [1.8, 1.9) : 5
Aestatura	6	-0.7333	2	0	1076	228	0.2119	0	Estatura que estima tener el encuestado [1.9, 2.0) : 6
Aestatura	7	1.928548	1	1	1076	228	0.2119	1	Estatura que estima tener el encuestado > 2.0) : 7
Apeso	1	-3.77209	62	1	1076	228	0.2119	0.0161	Peso que estima tener el encuestado <= 50 : 1
Apeso	2	-4.05811	79	2	1076	228	0.2119	0.0253	Peso que estima tener el encuestado (50, 55) : 2
Apeso	3	-5.74441	132	1	1076	228	0.2119	0.0076	Peso que estima tener el encuestado [55, 60) : 3
Apeso	4	-5.1211	172	9	1076	228	0.2119	0.0523	Peso que estima tener el encuestado [60, 65) : 4
Apeso	5	-1.86651	142	21	1076	228	0.2119	0.1479	Peso que estima tener el encuestado [65, 70) : 5
Apeso	6	-2.34173	138	18	1076	228	0.2119	0.1304	Peso que estima tener el encuestado [70, 75) : 6
Apeso	7	0.84116	106	26	1076	228	0.2119	0.2453	Peso que estima tener el encuestado [75, 80) : 7
Apeso	8	8.123762	143	70	1076	228	0.2119	0.4895	Peso que estima tener el encuestado [80, 90) : 8
Apeso	9	14.14686	102	80	1076	228	0.2119	0.7843	Peso que estima tener el encuestado >= 90 : 9
condi_act	1	5.045429	44	23	1076	228	0.2119	0.5227	¿Cómo consideras tu condición física actual? 1 : Muy mala
condi_act	2	5.865344	189	73	1076	228	0.2119	0.3862	¿Cómo consideras tu condición física actual? 2 : Mala
condi_act	3	-0.57931	429	86	1076	228	0.2119	0.2005	¿Cómo consideras tu condición física actual? 3 : Regular
condi_act	4	-4.18504	355	43	1076	228	0.2119	0.1211	¿Cómo consideras tu condición física actual? 4 : Buena
condi_act	5	-2.94241	57	3	1076	228	0.2119	0.0526	¿Cómo consideras tu condición física actual? 5 : Muy buena
condi_act	8	-0.7333	2	0	1076	228	0.2119	0	¿Cómo consideras tu condición física actual? 8 : No quiero re
condi1	1	3.176688	41	17	1076	228	0.2119	0.4146	¿Cómo consideras tu condición física hace un año? 1 : Muy n
condi1	2	4.71648	180	64	1076	228	0.2119	0.3556	¿Cómo consideras tu condición física hace un año? 2 : Mala
condi1	3	0.133941	396	85	1076	228	0.2119	0.2146	¿Cómo consideras tu condición física hace un año? 3 : Regula
condi1	4	-2.65254	367	57	1076	228	0.2119	0.1553	¿Cómo consideras tu condición física hace un año? 4 : Buena
Apuesto	5	-2.3817	32	4	1076	228	0.2119	0.0789	Puesto: Estudiante

Epsilon	# participantes	# obesos	Proporcion obesos	Puesto
-2.81	23			
1.23	74			
0.19	54			
-1.64	10			
-2.38	52			
-3.58	81			
-2.05				
2.03				
-0.53				
0.51				
2.41				
2.06				
3.53				
0.30				
2.85				



¿Cuántas calorías hay en un litro de agua?	Epsilon	# participantes	Proporcion poblacion	# obesos	Probabilidad obesidad	Proporcion obesos
No sabe el número de calorías que						

¿Cómo es tu salud actualmente?	Epsilon	# participantes	# obesos	Proporcion obesos
1 : Muy mala	1.15	15	5	33.33%
2 : Mala				
3 : Regular				
4 : Buena				
5 : Muy buena				

¿Qué acciones le gustaría tomar respecto a su salud?	Epsilon	# participantes	Proporcion poblacion	# obesos	Probabilidad obesidad	Proporcion obesos
Bajar de peso	5.25	771	71.65%	223	28.92%	97.81%
Esta contento con su peso	-7.54	239	22.21%	3	1.26%	1.32%
Subir de peso	-3.50	63	5.86%	2	3.17%	0.88%
No sabe	-0.90	3	0.28%	0	0.00%	0.00%

Proporcion obesos
31.18%
31.08%
19.38%
17.81%
22.36%
23.68%

Some Physiological Networks

Metabolic syndrome components

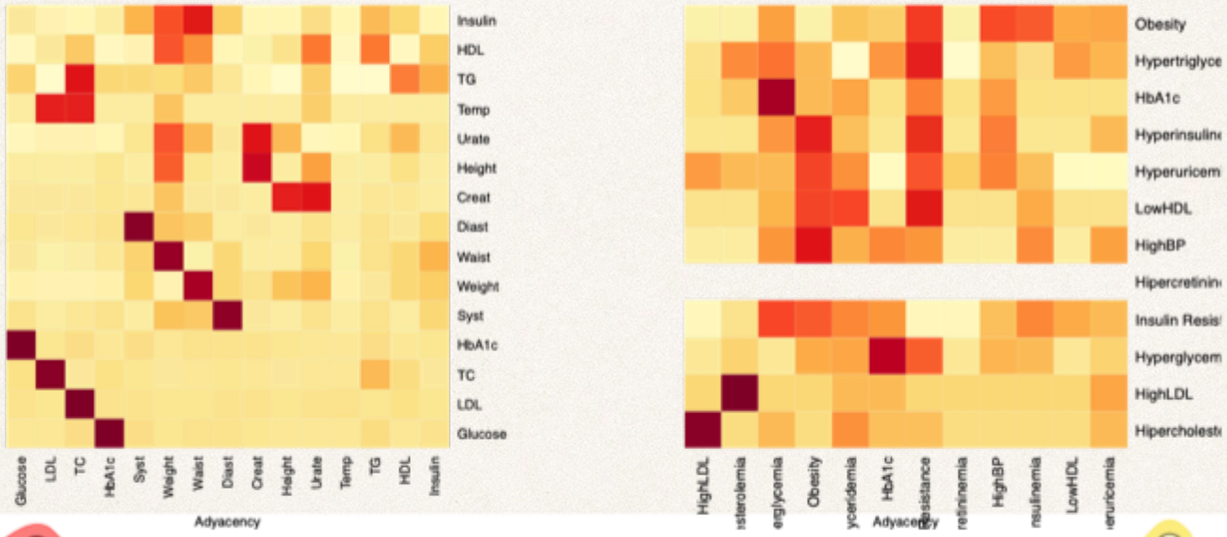
Physiological parameters

Pathological conditions

$$r_{xy} = \frac{\sum_{i=0}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=0}^{n}(x_i - \bar{x})^2}\sqrt{\sum_{i=0}^{n}(y_i - \bar{y})^2}}$$

$$\varepsilon = \frac{N_x\big(P(c|x) - P(c)\big)}{\sqrt{N_x\big(1 - P(c)\big)P(c)}}$$

Correlation matrix

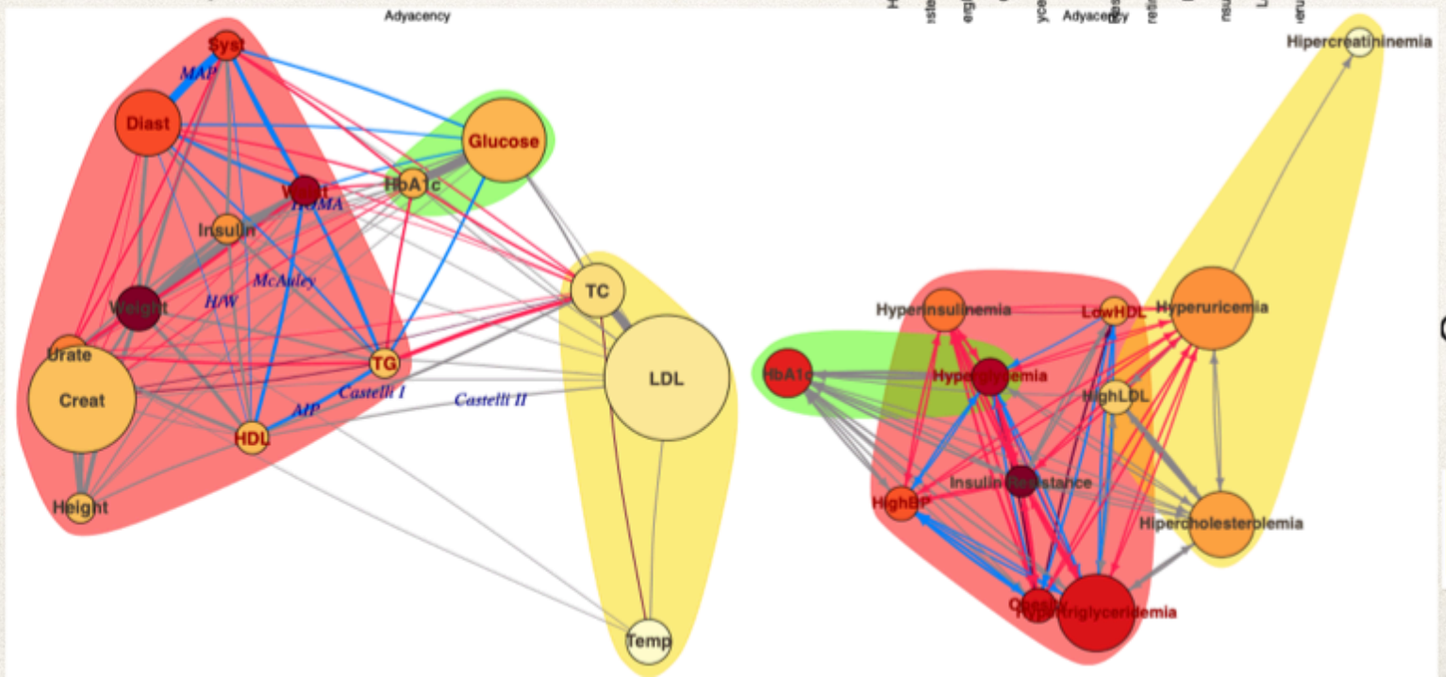


Largest clique

Metabolic syndrome

Farthest nodes

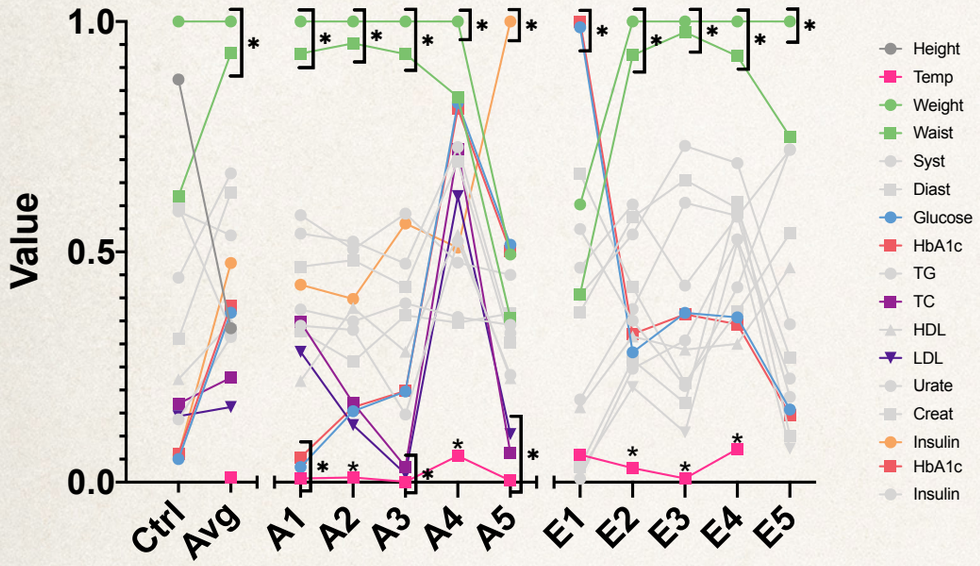
Network clustering



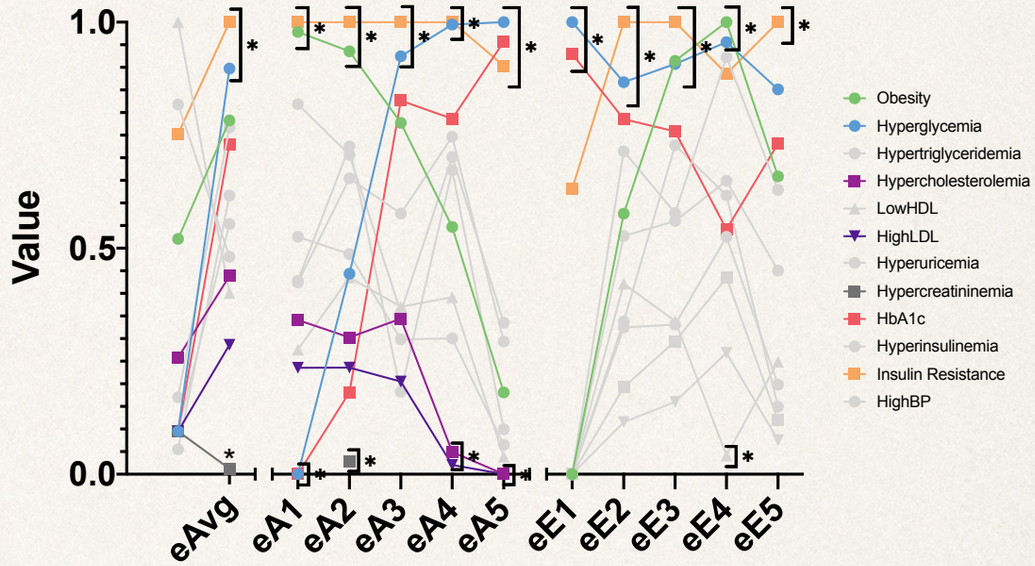
Network properties as a function of age (A1-A5) and education (e1-e5)

Quantity and quality of metabolic "wear and tear"

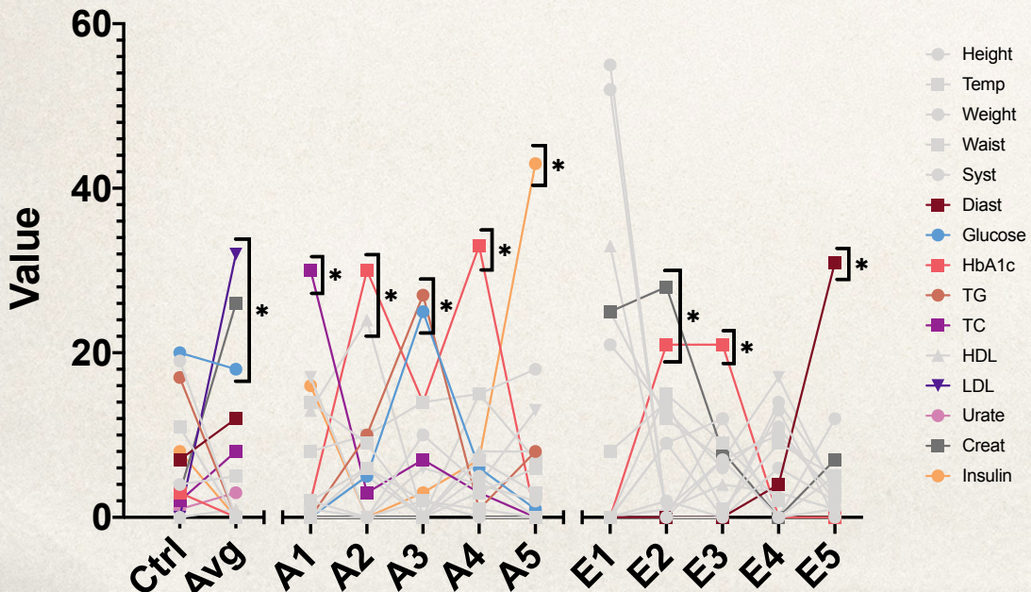
Eigencentrality (Pearson model)



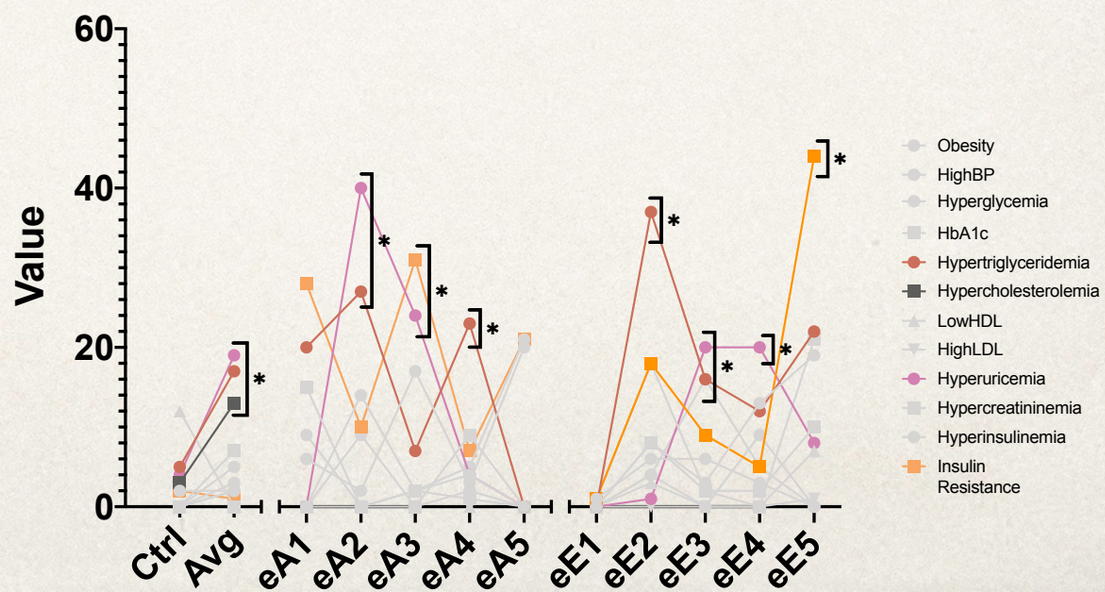
Eigencentrality (Epsilon model)



Betweenness (Pearson model)



Betweenness (Epsilon model)



Quantity and quality of metabolic “wear and tear”

Table 3. Binomial logistic regressions of anthropometric, blood pressure, and fasting blood test variables taking as class variable the at risk population using the cutoffs of supplementary material Table S1, for the independent variables education (Edu), BMI, age and sex.

Variable	N	Edu exp(b)	p	BMI exp(b)	p	Age exp(b)	p	Sex exp(b)	p
BMI	1073	0.681	0.000 **			1.021	0.001 *	0.946	0.726
WC (women)	689	0.700	0.000 **			1.042	0.000 **		
WC (men)	384	0.912	0.384			1.047	0.000 **		
SBP	1073	0.760	0.022 *	1.190	0.000 **	1.065	0.000 **	0.393	0.000 **
DBP	1073	0.939	0.491	1.167	0.000 **	1.038	0.000 **	0.614	0.016 *
PP	1073	0.848	0.507	1.129	0.004 *	1.061	0.011 *	0.382	0.087
Glucose	1072	0.926	0.306	1.101	0.000 **	1.055	0.000 **	0.910	0.580
Hb A1c	1068	0.767	0.034 *	1.095	0.000 **	1.064	0.000 **	1.544	0.150
Insulin	1072	1.068	0.679	1.203	0.000 **	0.985	0.276	0.609	0.125
HOMA-IR	1071	0.846	0.011 *	1.240	0.000 **	1.013	0.022 *	1.075	0.624
Uric acid (women)	689	1.025	0.832	1.106	0.000 **	1.016	0.115		
Uric acid (men)	383	0.856	0.140	1.110	0.000 **	0.994	0.480		
Triglycerides	1072	0.859	0.014 *	1.091	0.000 **	1.025	0.000 **	0.469	0.000 **
Total cholesterol	1073	0.993	0.907	1.008	0.549	1.041	0.000 **	0.880	0.335
HDL (women)	689	0.770	0.001 *	1.116	0.000 **	0.983	0.012 *		
HDL (men)	384	0.737	0.002 *	1.065	0.007 *	1.002	0.797		
LDL	1070	0.986	0.813	1.009	0.489	1.037	0.000 **	0.805	0.109
Metabolic Syndrome	1073	0.827	0.005 *	1.202	0.000 **	1.036	0.000 **	0.960	0.789

* indicates statistically significant at the $p < 0.05$ level.
** indicates statistically significant at the $p < 0.001$ level.

Quantity and quality of metabolic "wear and tear"

Table 4. Multiple linear regressions of anthropometric, blood pressure, and fasting blood test variables using education (Edu), BMI, age and sex as independent variables.

Variable	N	Edu	p	BMI	p	Age	p	Sex	p
Height	1073	0.015	0.000 **			-0.001	0.000 **	-0.127	0.000 **
Weight	1073	-1.287	0.000 **			0.077	0.014 *	-13.127	0.000 **
BMI	1073	-1.03	0.000 **			0.076	0.000 **	-0.758	0.014 *
WC (women)	689	-2.389	0.000 **			0.206	0.000 **		
WC (men)	384	-0.804	0.141			0.207	0.000 **		
SBP	1073	-0.331	0.383	1.009	0.000 **	0.315	0.000 **	-4.493	0.000 **
DBP	1073	-0.099	0.727	0.707	0.000 **	0.164	0.000 **	-3.047	0.000 **
PP	1073	-0.232	0.387	0.302	0.000 **	0.150	0.000 **	-1.446	0.015 *
Glucose	1072	-2.068	0.028 *	0.733	0.000 **	0.592	0.000 **	-0.255	0.902
Hb A1c	1068	-0.137	0.000 **	0.030	0.000 **	0.030	0.000 **	0.119	0.107
Insulin	1072	-0.320	0.051	0.594	0.000 **	-0.012	0.371	-0.175	0.628
HOMA-IR	1071	-0.115	0.036 *	0.177	0.000 **	0.008	0.096	-0.029	0.813
Uric acid (women)	689	0.039	0.317	0.073	0.000 **	-0.001	0.668		
Uric acid (men)	383	-0.128	0.028 *	0.090	0.000 **	-0.006	0.256		
Triglycerides	1072	-9.909	0.001 *	3.827	0.000 **	1.183	0.000 **	-41.313	0.000 **
Total cholesterol	1073	1.061	0.363	-0.005	0.983	1.004	0.000 **	-2.428	0.346
HDL (women)	689	1.926	0.000 **	-0.733	0.000 **	0.097	0.011 *		
HDL (men)	384	1.428	0.001 *	-0.408	0.000 **	0.018	0.613		
LDL	1070	0.973	0.323	-0.114	0.594	0.677	0.000 **	-1.520	0.483

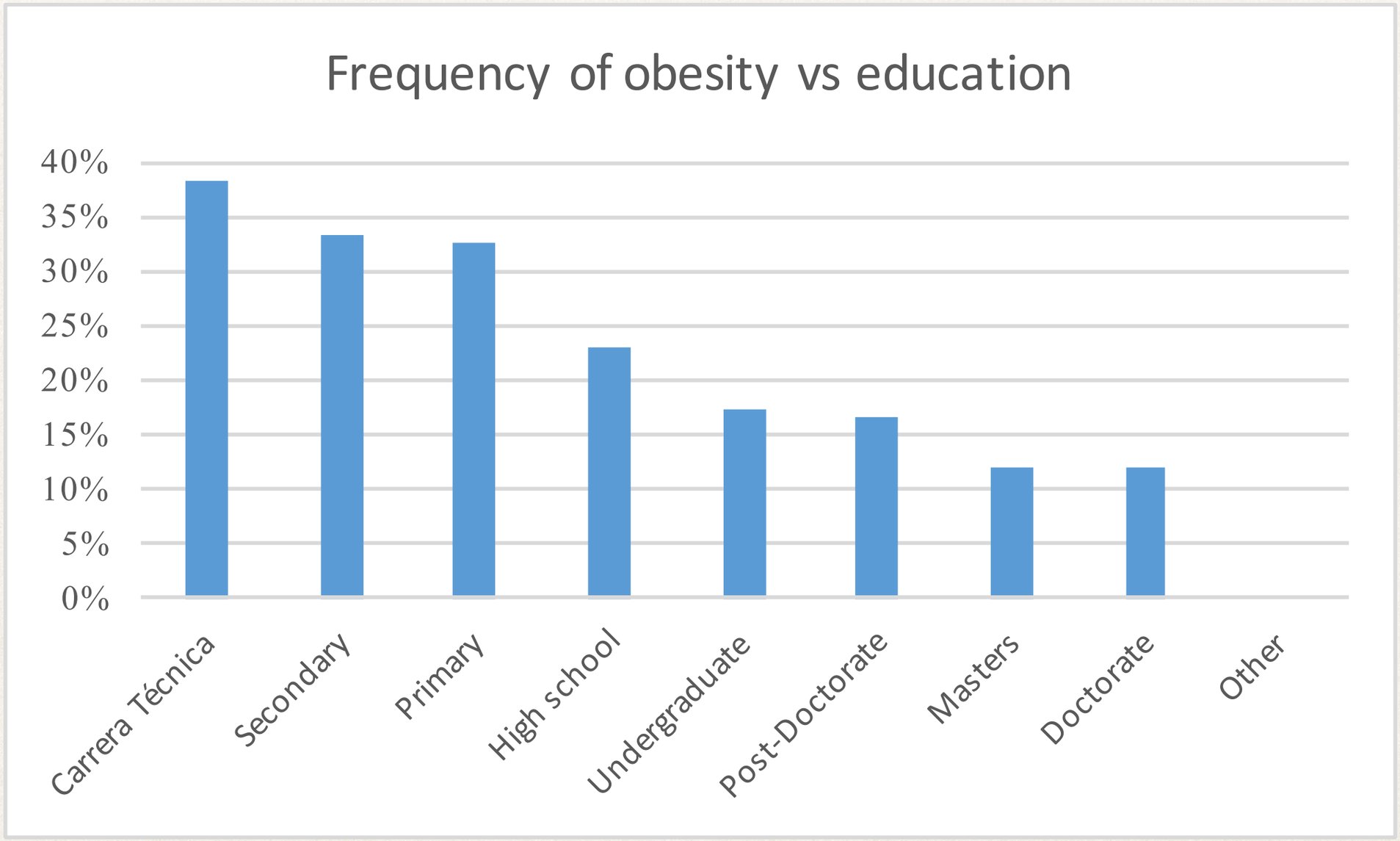
* indicates statistically significant at the $p < 0.05$ level.
** indicates statistically significant at the $p < 0.001$ level.

Quantity and quality of metabolic "wear and tear"

Table 5. Profiles of the metabolic risk factors for the risk factors: Education (E), BMI (B), Age (A) and Sex (S) as determined from the odds ratios of the logistic regressions using the thresholds of supplementary material Table S1, and multiple linear regressions. * denotes that the corresponding factor indicates the same relation but is not significant at the 95% confidence level with this sample size. Bolface indicates those variables that enter in the definition of MS.

Metabolic variable	Profile logistic	Profile linear
WC - women	EA	EA
WC - men	E*A	E*A
SBP	EBAS	E*BAS
DBP	BAS	BAS
Glucose	E*BA	EBA
Hb A1c	EBA	EBA
Insulin	B	B
HOMA-IR	EBA	EBA*
Uric acid - women	B	B
Uric acid - men	E*B	EB
Triglycerides	EBAS	EBAS
Total cholesterol	A	A
HDL - women	EBA	EBA
HDL - men	EB	EB
LDL	A	A

Obesity and educational level



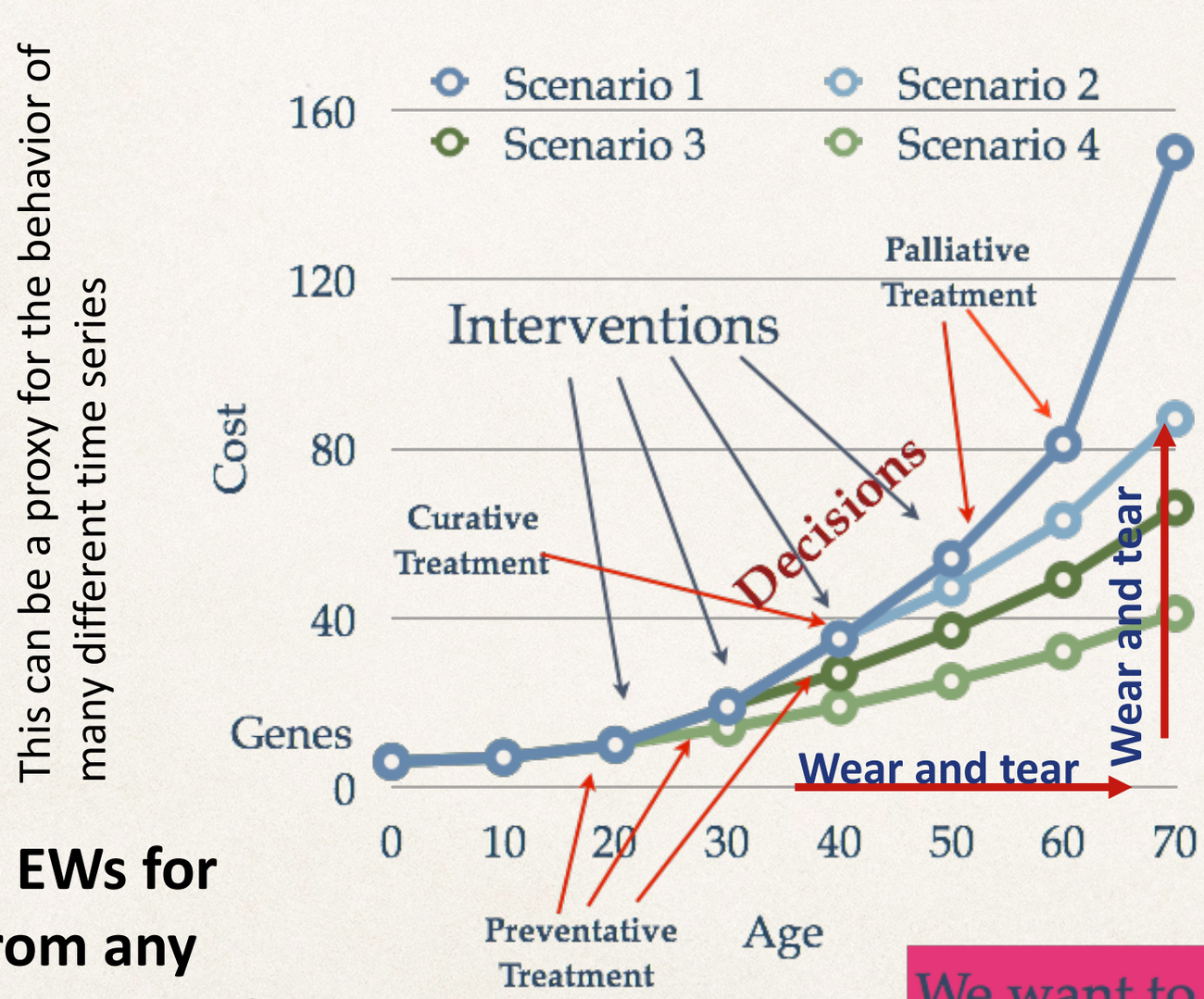
UNAM 2014 Study: 1,076 participants

Physiological variables and networks change as a function of age and education —> they change due to decisions ("bad" versus "good"), i.e., due to behaviour

The Problem of Behaviour is the Problem of Adaptation

Time series are adaptive

Associated with conduct and decision making



Scenario 1: Onset of obesity at 20
Continued obesity and onset of metabolic syndrome at 40
Onset of diabetes at 50
Onset of renal failure at 60
Death at 70

Scenario 2: Onset of obesity at 20
Continued obesity and onset of metabolic syndrome at 40
Onset of diabetes at 50
Adequate control and treatment of comorbilities at 60
Bad health and high cost at 70

Scenario 3: Overweight at 20
Obesity at 40
Onset metabolic syndrome at 50
Onset of diabetes at 60
Continued diabetes but no serious comorbilities at 60
Ill health and moderate cost at 70

Scenario 4: Overweight at 30
Obesity at 50
Onset of metabolic syndrome at 60
Onset of diabetes at 70 but relative health

There are EWs for passing from any one state to any other

Early warnings

We want to predict and understand "histories"

What is a "normal" versus an "optimal" trajectory?

What Doesn't Make Decisions?

Prediction and science: the last 3 centuries

In fact…

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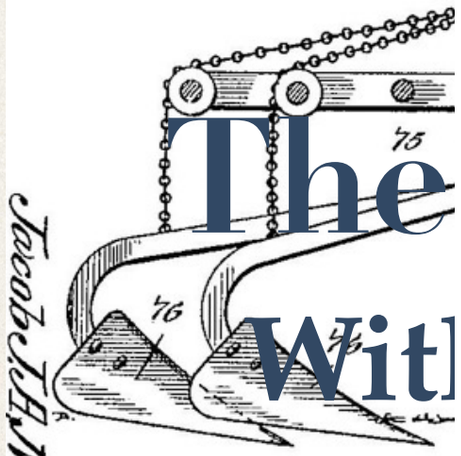

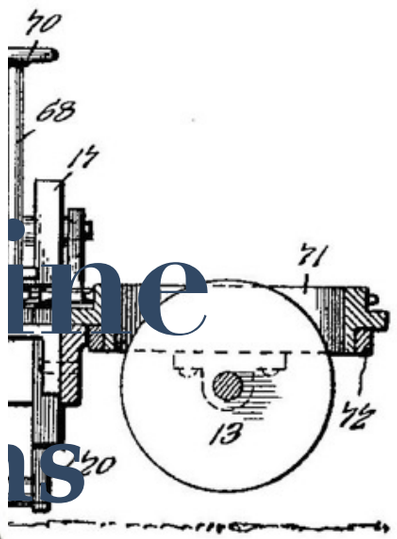

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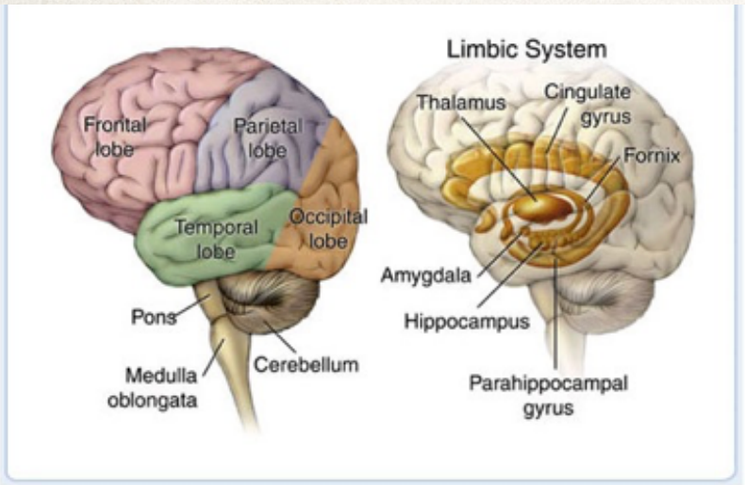
we are slaves to the law

The Conductome

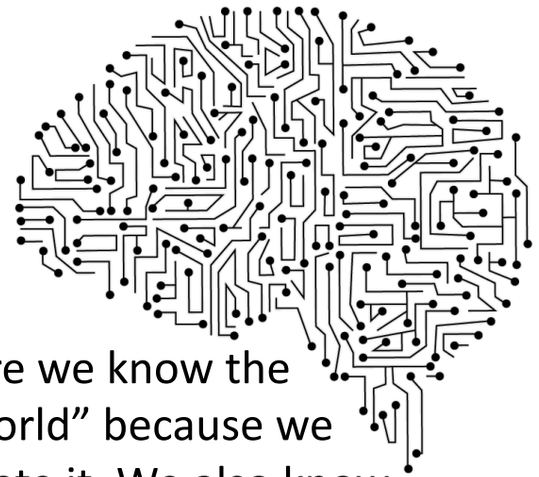


Here we neither know the ”World” nor the algorithm P(|) nor the payoff from our prediction and action

This…

$$P(C(t) \mid \underline{X}(t))$$

Decision/Action **The “World”**



Here we know the ”World” because we create it. We also know the algorithm P(|) and the payoff from our prediction and action

is the

CONDUCTOME

“World” + algorithm +payoff

In Evolution Natural Selection is the ultimate arbiter of the “value” of decisions

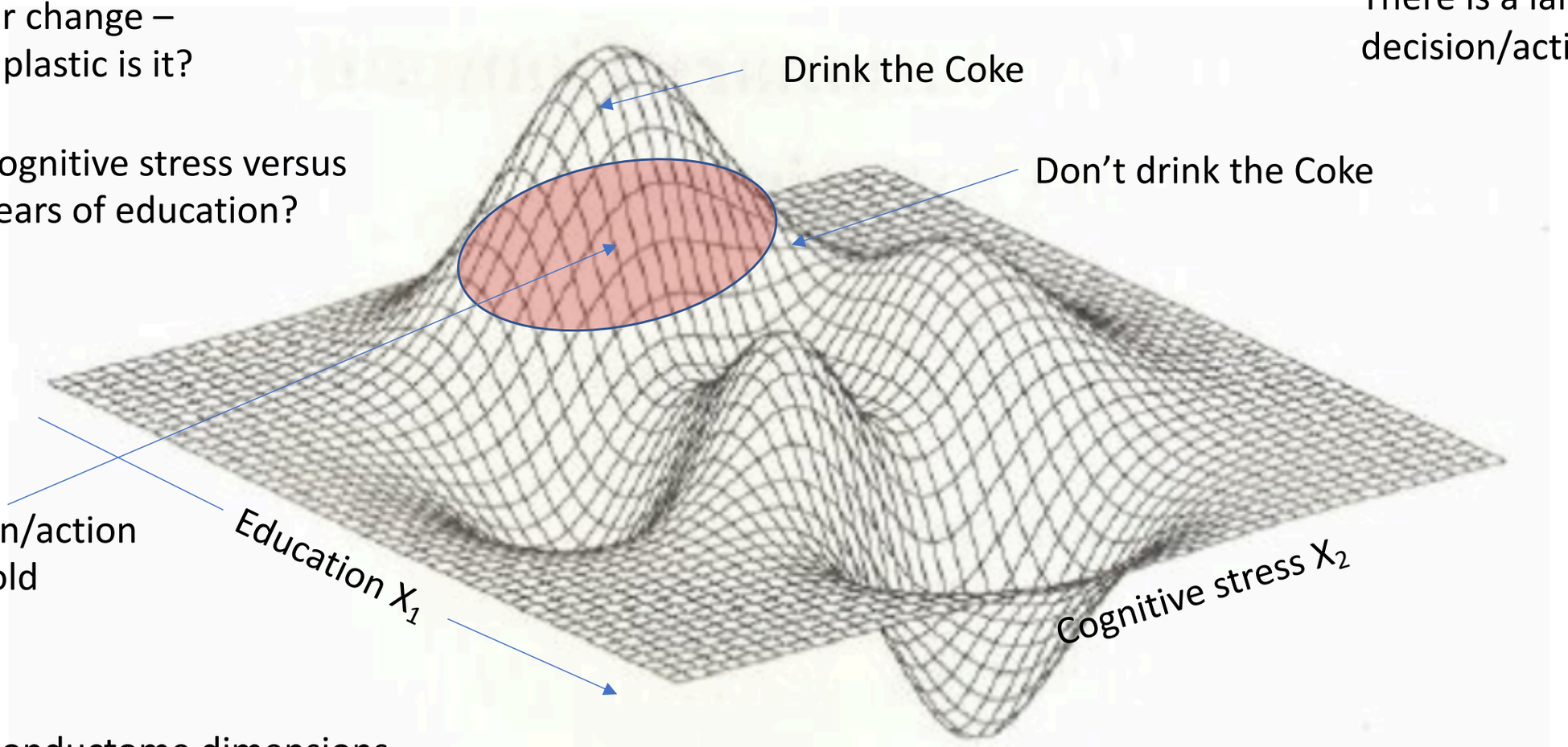
The Conductome also implicitly represents a Prediction Model where the prediction is that the decision/action will lead to some benefit.

The Conductome Landscape

The Conductome landscape is dynamic and adaptive. There is a landscape for every decision/action/behaviour

Behaviour change –
Just how plastic is it?

Reduce cognitive stress versus
5 more years of education?



(X_1, X_2) – Conductome dimensions

Decision making and obesity

You can't gain weight without a set of decisions/ actions that correspond to a behaviour

1. What are those behaviours?
2. How do we measure them?
3. What are risk factors for them?
4. How does physiology affect them and how do they affect physiology?
5. How plastic are they?
6. How do we model them?

Metabolic changes occur because Ein > Eout

Why is Ein > Eout?

Energy “needed”

Activity

Behaviour:
Direct and
Indirect

BMR

Behaviour:
Indirect

Heat generation

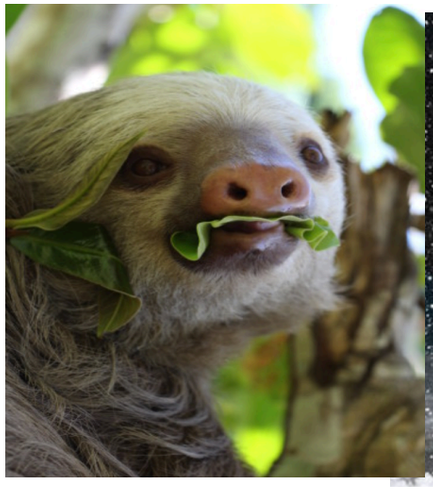
Behaviour:
Direct and
Indirect

Need versus
Behaviour versus
Environment

Needed for what?

This is dependent on the environment both

now and in the future

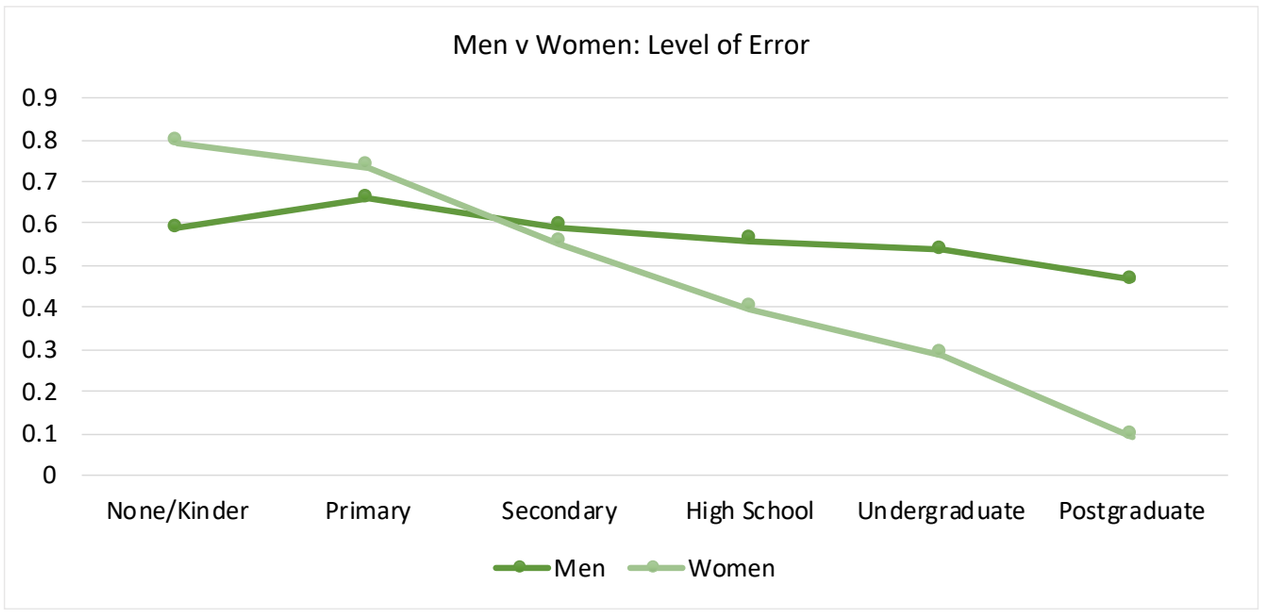


A Conductome variable for obesity: Body Image

Why are we so overweight? We don't predict very well our "body state"

What does the Conductome represent?

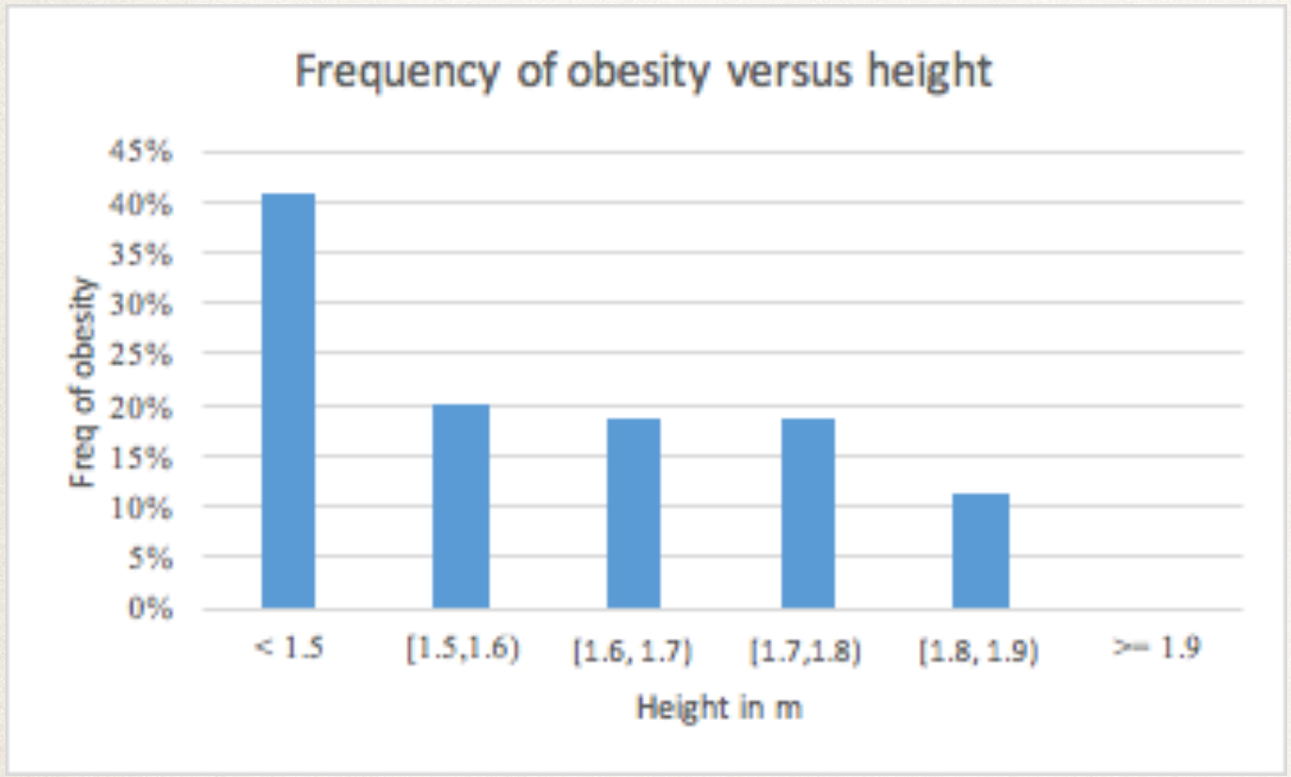
The difference between them depends on many factors, e.g. educational level
And has consequences…



1) "In the last year have you lost or gained weight?"
2) "Was this weight loss intentional?"

BMI Obese	Education level (n; %)					
Intention to lose	None/Kinder	Primary	Secondary	High School	Undergraduate	Postgraduate
All	17; 6.3	100; 7.1	61; 9.2	28; 10.9	24; 15.7	2; 25.0
Men	2; 3.9	23; 8.0	10; 6.4	10; 12.2	10; 16.1	1; 25.0
Women	15; 6.8	77; 6.8	51; 10.0	18; 10.3	14; 15.4	1; 25.0

A Conductome variable for obesity: Portion size



Why are shorter people more likely to be obese?

Big Mac meal
for a large person

Big Mac meal
for a short person

Torta Cubana
for a large person

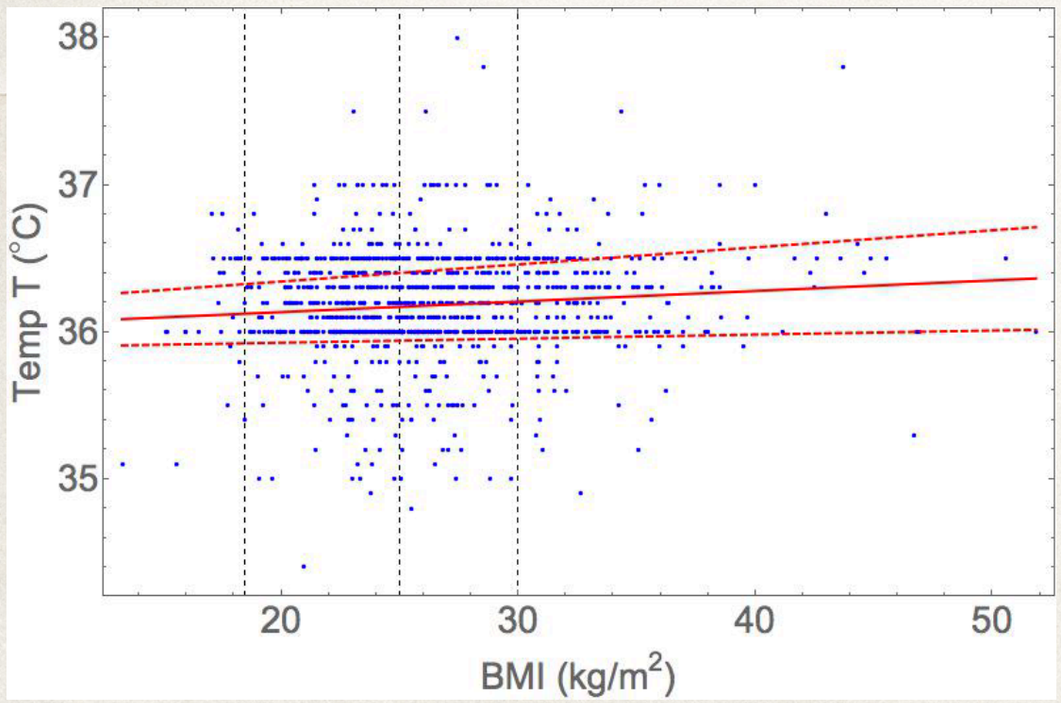
Torta Cubana
for a short person

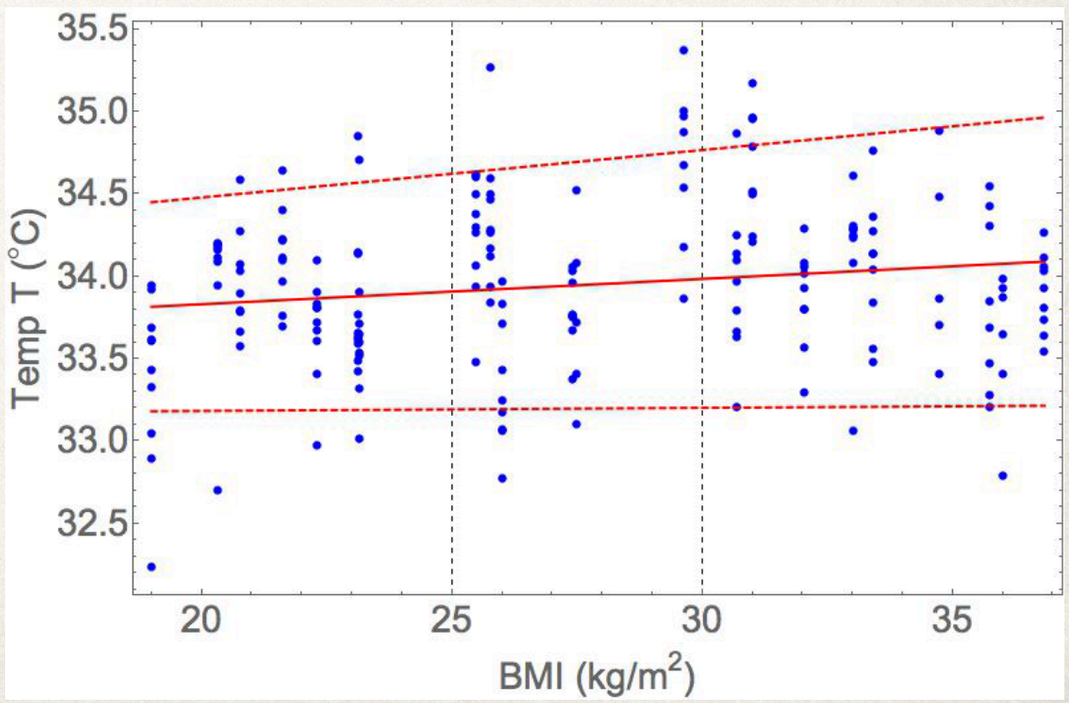
A Conductome variable for obesity: Temperature

Why aren't we even more overweight?

Hypothesis: Human physiology is equipped to resist "wear and tear" and has multiple autonomous mechanisms to maintain homeostasis. For example…

	Study 1		Study 2	
	points	**deciles**	**7-day mean**	**1-day mean**
slope	0.0072	0.0067	0.0093	0.015
intercept	35.99	36.00	33.69	33.524
CIslope	0.0028	0.0024	-0.019	0.0019
	0.012	0.011	0.038	0.029
Clintercept	35.88	35.89	32.88	33.15
	36.11	36.12	34.51	33.90
tslope	3.18	3.56	0.68	2.25
tintercept	590.34	708.93	86.9	174.92
F	10.15	12.64	0.46	5.06
p	0.0015 (*)	0.0074 (*)	0.50	0.026 (*)
R2	0.0094	0.61	0.022	0.027





Agent Based Models for the Study of Food Strategy in Obesogenic Environments

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Introduction

Obesity and Overweight are complex phenomena with genetic, endocrine and behavioral components (Bray 2007). The positive ***Energy Imbalance*** that gives place to overweight occurs when consuming more energy than is spent. Consuming food involves ***Decision Making*** restricted by availability of sources, time and competition. The main objective of a ***Food Strategy*** is survival of individuals and populations. Then avoid negative long-term energy imbalance is a priority.

An optimal strategy seeks energy balance. It can regulate consumption, perception and movement across the environment. Nonetheless the extended epidemic of obesity and overweight is evidence of a generalized deviation of an optimal energetic plan.

Johnson and Andrews (2010) suggest a prehistoric mutation of human ancestors to increase fat stores. Such that mechanism, originally a survival advantage against starvation, could explain partially the resilient tendency to overweight in ***Obesogenic Environments***. There is no accessible data to test directly such that hypothesis. However those inaccessible scenarios can be investigated in a generative manner by agent system simulations (Epstein 2006).

The aim of this work is to investigate the origin and development of bias in food strategies with ***Agent Based Modeling*** (ABM). The Agent Model presented here exhibits the competition between two kind of agents: A perceptive one (Type II) that can observe a larger local environment at an energetic cost and other that only can perceive for free the cell where is situated (Type I). Agents were provided with three capacities: To eat, to move and to reproduce themselves. Perceptive agents' strategy is more complex and can be considered cognitively superior. To measure system's performance we obtain in each simulation the extinction time (if is the case), the final fraction of agents of type I and the time when diversity is lost (if is the case).

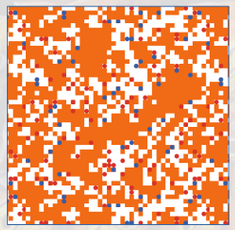
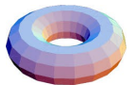


Figure 1. View of a typical simulation of ABM. This was implemented in NetLogo.

Design of Agents System

- Environment: 41 X 41Square Grid in a Thorus (PBCs), each cell can grow a ***source of energy***.
- Agents: Two types according food strategy: ***Perceptive*** and ***non-perceptive***.
- Agents have move, eat and intend to reproduce every time.
- Each time-step agents spent energy in a basal metabolism and in a cost of movement proportional to their energy. If the agent is perceptive pays a fixed cost of perception. Both agents consume the energetic sources in their consuption area.



Agent Type I (non-perceptive)

- Perceives only the cell where is placed
- Eat only the sources in the cell is placed (A = 1).
- Moves randomly to a neighbour cell

Agent Type II (perceptive)

- Perceives the cell where is placed and the first eight neighbours
- Eat only the sources in the cell is placed(A = 1).
- Moves to a neighbour cell with energetic sources available. It reduces uncertainty when looking for energy but it has a cost.

$$E_\alpha(t) = \begin{cases} \left(E_\alpha(t-1) - M_b + A^{(I)}E_s\right)\left(1 - C^{(m)}\right), & \text{if } \alpha \text{ is type I} \\ \left(E_\alpha(t-1) - M_b - \Delta M^{(p)} + A^{(II)}E_s\right)\left(1 - C^{(m)}\right), & \text{if } \alpha \text{ is type II} \end{cases}$$

Figure 2. Sketch of ABM environment, agent type I and II and Energy of agent at time t.

Parameters	Symbol
Basal Metabolism	M_b
Cost of Perception	$\overline{\Delta M}^{(p)}$
Cost of Movement	$\bar{C}^{(m)}$
Source Energy	E_s
Consumption Area	$A^{(I)}, A^{(II)}$

Table 1. Parameters and symbols of ABM.

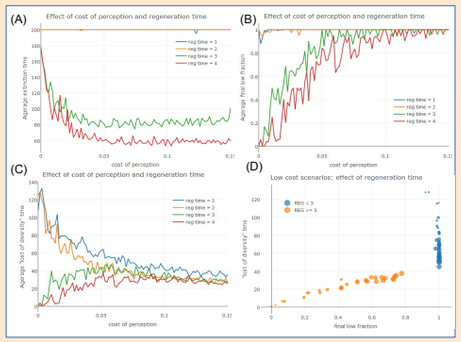


Figure 3. Effect of cost of perception and regeneration time in (A) average extinction time, (B) average final low fraction (type I fraction), (C) average time of lost of diversity and (D) comparison of rapid and slow regeneration on final fraction and lost of diversity time.

Figure 4. Effect of cost of movement and reproduction in (A) average final low fraction (type I fraction) and (B) histogram of final low fraction.

Effect of Cost of Perception and Regeneration of Sources

- Rapid regeneration of resources can make the population survive indefinitely (Fig. 3A). This also causes the scenarios with perceptual agents to disappear while slow regeneration allow diversity in the ensemble of simulations (Fig. 3B).
- Final stages where both type of strategies coexist are scarce. Most scenarios finish with homogeneous populations.
- Perceptive agents can live longer than non-perceptive only if the cost of perception is low (Fig. 3B). In those scenarios with rapid regeneration an increase in cost of perception makes the minority agents (perceptive) to dissapear faster. If regeneration is slow an increase on the cost makes the minority agents to dissapear a little bit more slowly (Fig. 4B).

Cost of movement and reproduction

- Reproduction consists in the division of an agent when it exceeds a limit of energy (20). It makes more pronounced the effect of the cost of movement in the final distribution of agents: This favors one of the two types depending on their value: If the cost of movement is lower than 0.02 agents type II are predominant. When is greater than 0.02 agents type I survive more oftenly (Fig. 4A).
- In general, reproduction changes changes the distribution of types in final states (Fig. 4B)
- The dynamics of the types distribution have a similar characteristic behavior: Cost of movement determines the final type of agent and reproduction helps the predominant agent (Fig. 5).

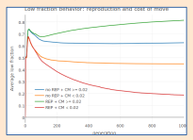


Figure 5. Effect of cost of movement and reproduction in the average fraction of type I agents at every generation.

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Let's try and recreate the world of 200,000 years ago and see what behaviours were useful in environments then versus environments now.

Recreate environments with scarcity / plenty and find which adaptations are favoured / disfavoured

Conclusions

- Human physiology has rhythms. Those rhythms have evolutionary origins. Those rhythms are affected by our decisions - our behaviour.
- The Human Conductome is the entirety of factors which control human behavior: **Behaviour <— Strategies <— Decisions <— Predictions**
- It is extraordinarily multifactorial and adaptive. It requires big, deep data across multiple scales to understand it: genetics, epigenetics, physiology, psychology, neuroscience, epidemiology, sociology,… We don't have such data, but the Data Revolution is helping.
- A crucial ingredient of the Conductome is how we evaluate decisions, the different concepts of value and to understand why we make "bad" decisions.
- Another crucial ingredient is how we create a model of reality that may be substantially different from reality itself. Such deviations can have severe psychological, social and other health consequences.

The goal of Project 42 is to obtain and model data in order to better understand the Conductome and predict human behavior. We have a lot of interesting work to do over the coming months, years, decades,… We need a lot of help!

You're all invited!

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What's my line?

What's my line? I'm an elementary particle - I have electric charge -1, etc.
I'm a species, I have barcode (of life), I am a mammal,…

- All systems are characterised by important "labels"
  - **Physics**: electric charge, mass, dipole moment, crystal structure, volume, pressure, temperature,…
    - Physical systems have **very** few relevant labels and we know, generally, what they are
  - **Biology**: uni-celular/multi-celular, male, female, old young, claws, cold/warm blood, egg laying/live birth, rich, poor, British/Bulgarian/Australian, single/married, mother/father, lung, heart, chin, brain, organ, hypothalamus, Akt, obese, diabetic, Parkinson's,…
    - Biological systems have an enormous ("uncountable") number of potentially relevant labels and each label is associated with both a structure and a function
- Labels are contextual - they characterise interactions
  - What is an interaction?
    - When the participants in the interaction have space-time trajectories that are different compared to the absence of the interaction (null hypothesis).
    - Interactions have associated labels - Electric charge of an electron has no meaning other than with respect to its behaviour relative to another charged object
  - There are very few fundamental interactions because there are very few fundamental labels
  - In biological systems there are an enormous number of interactions because there are an enormous number of relevant labels
  - Labels can evolve in time (iron nucleus versus diabetic) as a new state emerges from a previous one

What's my scale?

- All systems are characterised by important spatial or temporal scales
  - Physics: gravity (Planck time/scale), grand unification, electroweak scale, nuclear, atomic, molecular, macro-molecular, solid state, weather, geological/planetary, astrophysical, cosmological.
  - Biology: cellular (Adella), physiology (day, month, year), lifetime (genetic), extinction (different taxonomic levels)
  - Language: letter, syllable, word, phrase, sentence, paragraph, chapter, article, book.
- What you can say about an interaction depends on the space/time scale over which it is observed
- In physics there is usually a dominant interaction at a given scale with associated effective degrees of freedom. There is little cross-talk between scales

Biorhythm Scales

- From intra-cellular signaling
- to inter-cellular signaling
- to organ/organ signaling
- to environment/organ interactions
  - behavior: foraging, eating, sleep, etc.
- to behavior change and
- Evolution

ms vs sec vs mins vs hours vs days vs weeks vs years vs…
“micro” versus “macro” homeostasis

What is the nature of the corresponding time series?
What is the natural variational scale?
What is the natural coarse graining scale?
When does the time series reflect adaptive versus ”deterministic” behavior?
Does it reflect homeostasis? (Over what time scale?)

What is important in a time series?

The mean, the median, the variance, the frequency, the amplitude, the 27th moment,…?

(“Can you hear the shape of a drum?” and Efficient markets theory)

What's my (statistical) ensemble?

- Observations: Longitudinal (how long) versus transverse - both
  - Multitude of labels problem (multi-factoriality)
- What can you say about those observations?
  - What information is contained there?
- We deduce the nature of interactions from ensembles of observations principally associated with where something is in space and time (both Plamen and Adella),
  - "co-occurrences" in space and/or time relative to a null hypothesis is a measure of interaction
- There are too many labels to deduce the nature of interactions in biological systems by "divide and conquer"

Heterogeneity of homeostasis

glucose stdev	glucose av	tbg stdev	tgb av	chol stdev	chol av	HOMA stdev	HOMA av
33.82	96.95	115.08	165.72	42.12	201.86	2.13	2.13
Variation factor	2.87	Variation factor	1.44	Variation factor	4.79	Variation factor	1.00
hdld stdev	**hdld av**	**uric stdev**	**uric av**	**crs stdev**	**crs av**		0.41
12.34	47.57	2.33	5.44	0.42	0.81		
Variation factor	3.86	Variation factor	2.34	Variation factor	1.95		
ldl stdev	**ldl av**	**hba stdev**	**hba av**	**insulina stdev**	**insulina av**		
56.58	122.47	1.29	5.35	6.41	8.44		
Variation factor	2.16	Variation factor	4.16	Variation factor	1.32		