The Human Conductome:
A New Paradigm for Understanding Human Obesity

Christopher R. Stephens

C3 – Centro de Ciencias de la Complejidad y Instituto de Ciencias Nucleares, UNAM

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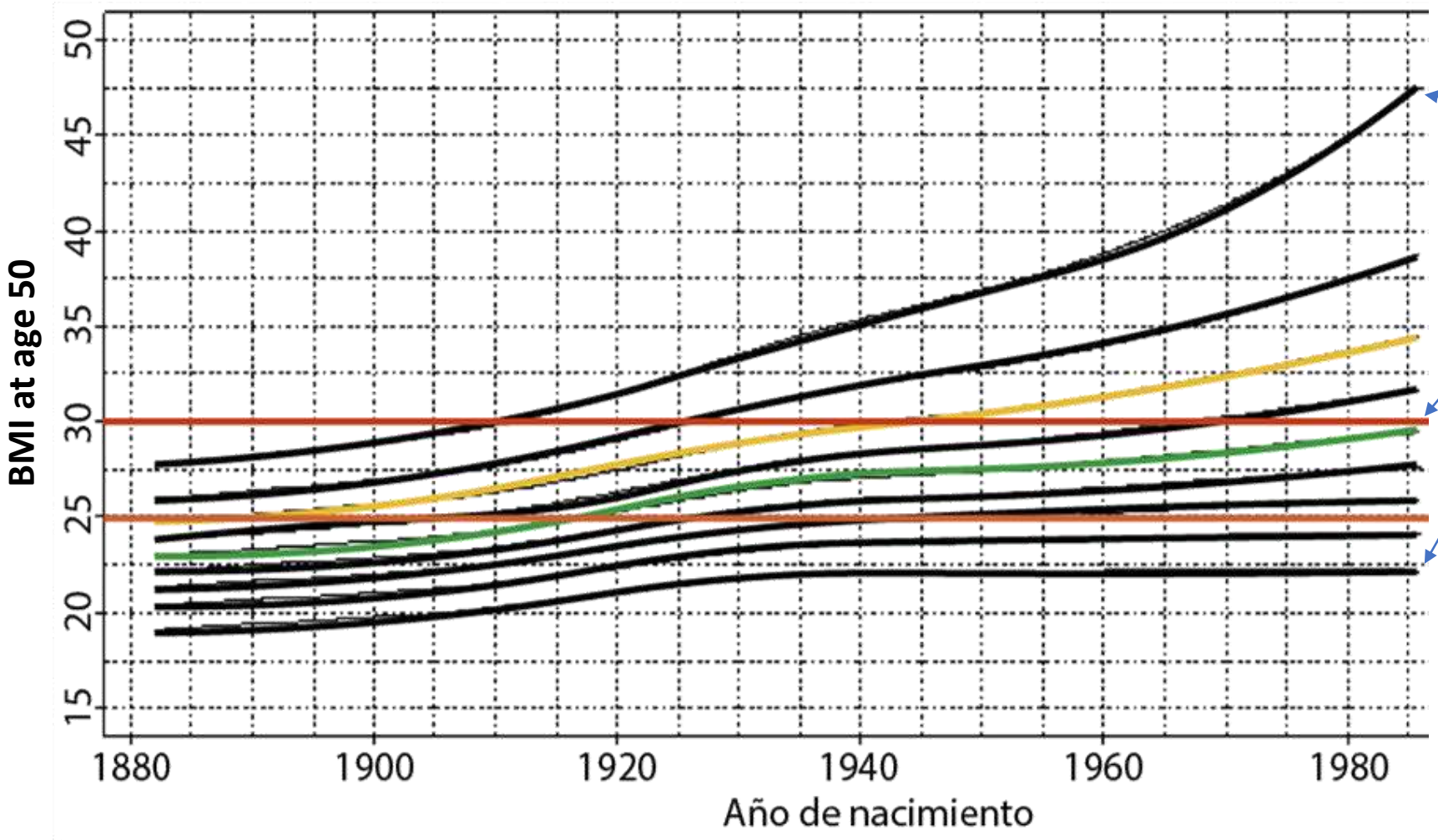
Is there a *recent* obesity epidemic?

Yes… and no

Deciles trends in white US males by birth cohort



BMI Deciles

90th

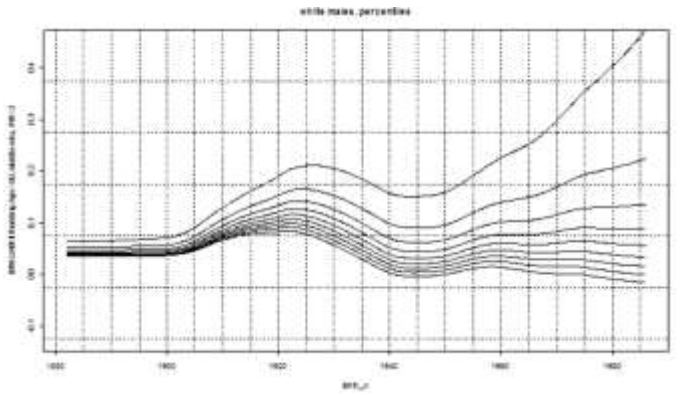
50th

10th

What factors (behaviours) are at the root of these differences?

Radical differences!

Rate of change of deciles trends



Remember: Evolution likes diversity

Komlos, J., & Brabec, M. (2010). The Trend of Mean BMI Values of US Adults, Birth Cohorts 1882-1986 Indicates that the Obesity Epidemic Began Earlier than Hitherto Thought. doi: 10.3386/w15862

Why is there obesity?

Eat to live not live to eat!

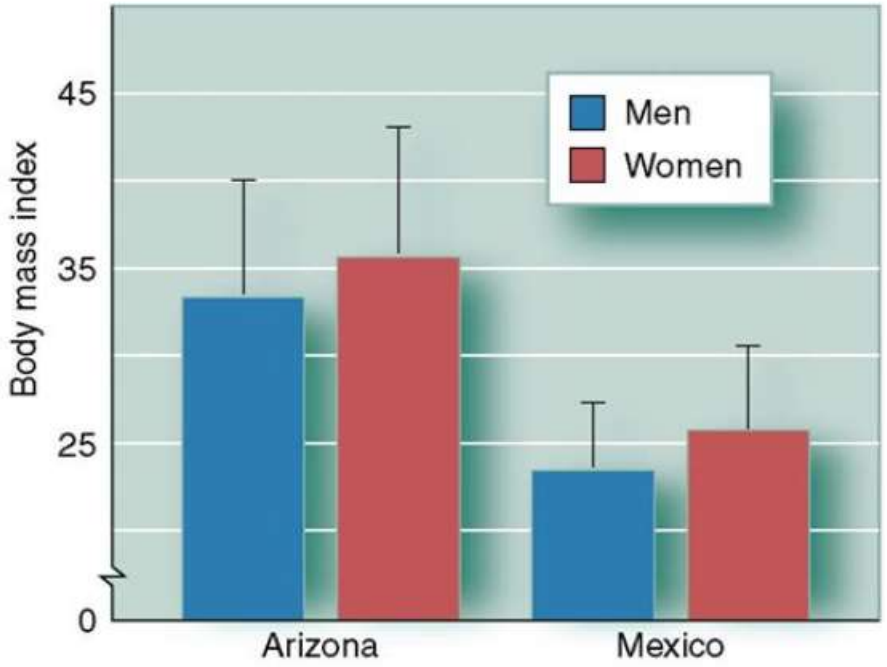
Nature versus nurture versus environment

Nature?

TABLE 2
Intraclass twin correlations (and 95% CIs) for BMI and waist circumference SD scores[1]

Measure	MZall (n = 1813)	DZall (n = 3279)	DZss (n = 1658)	DZos (n = 1621)
BMI	0.86 (0.85, 0.87)	0.49 (0.47, 0.51)	0.51 (0.48, 0.53)	0.47 (0.45, 0.50)
Waist	0.85 (0.84, 0.86)	0.48 (0.46, 0.50)	0.51 (0.49, 0.54)	0.45 (0.42, 0.48)

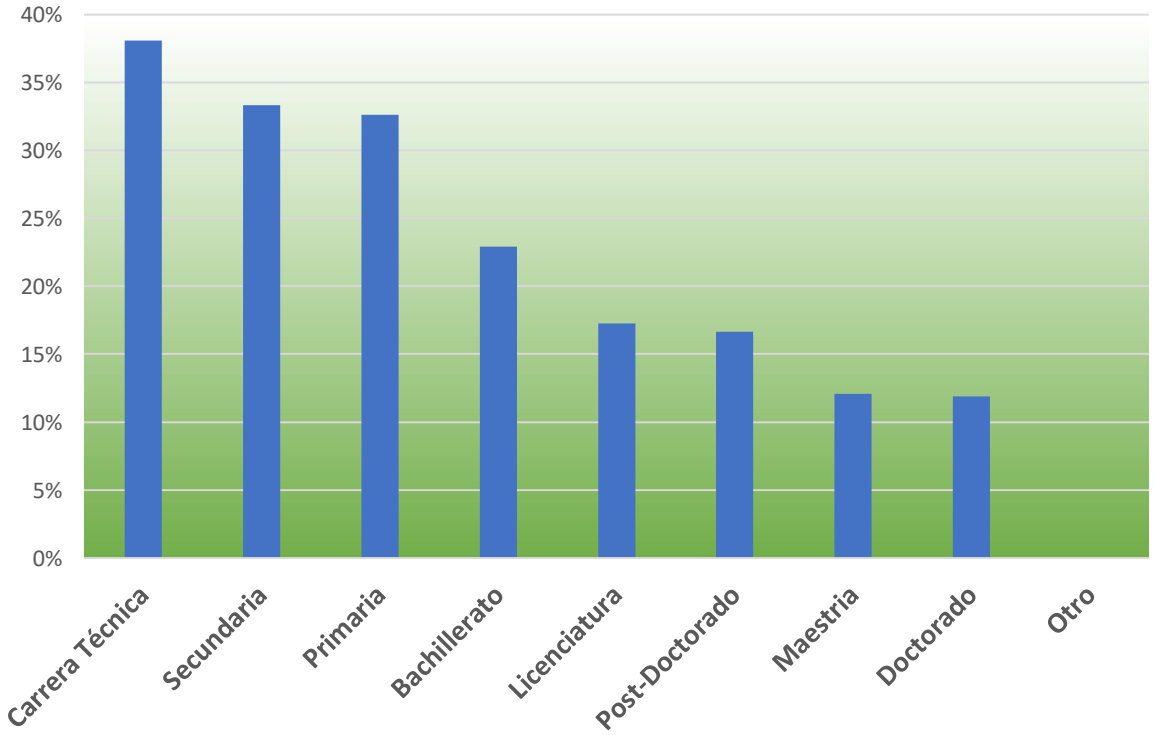
[1]MZall, monozygotic twins; DZall, dizygotic same-sex and opposite-sex twins; DZss, same-sex dizygotic twins; twins; DZM, dizygotic male twins; DZF, dizygotic female twins. All values were significant, $P < 0.001$.



The BMI for Pima Indian men and women living in Arizona and in northern Mexico (2006)

Nurture + environment?

Obesity incidence Project 42 UNAM

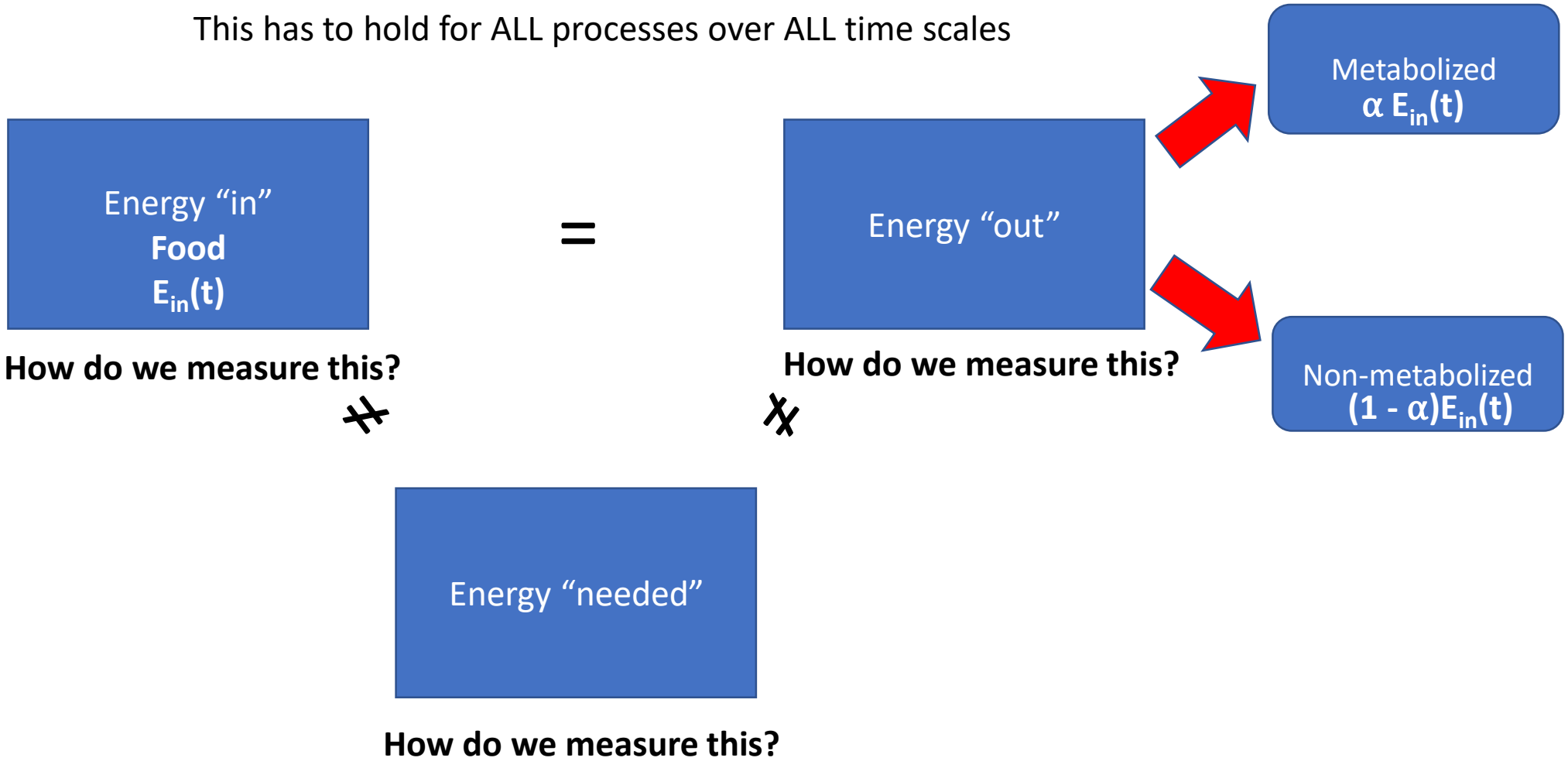


As a physicist... I have to say Energy Balance

This should almost be a tautology

Conservation of Energy

This has to hold for ALL processes over ALL time scales



And what does "Needed" mean anyway?

Energy “in”
Food

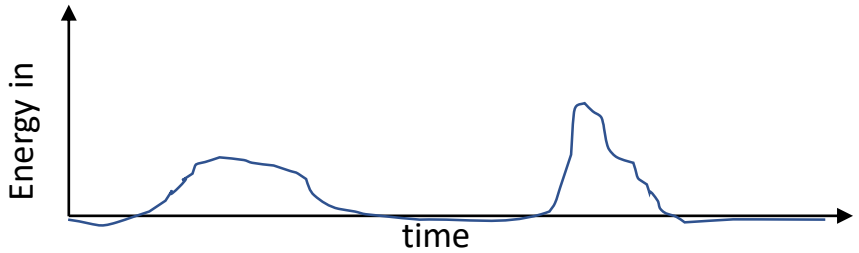
Behaviour in a given environment controls how much and what

Two principal dimensions: **Quantity** and “**Quality**”

How do we measure it?

The **gross energy** measured through bomb calorimetry is an upper limit on extractable energy

Standard calorie values try to account for digestibility



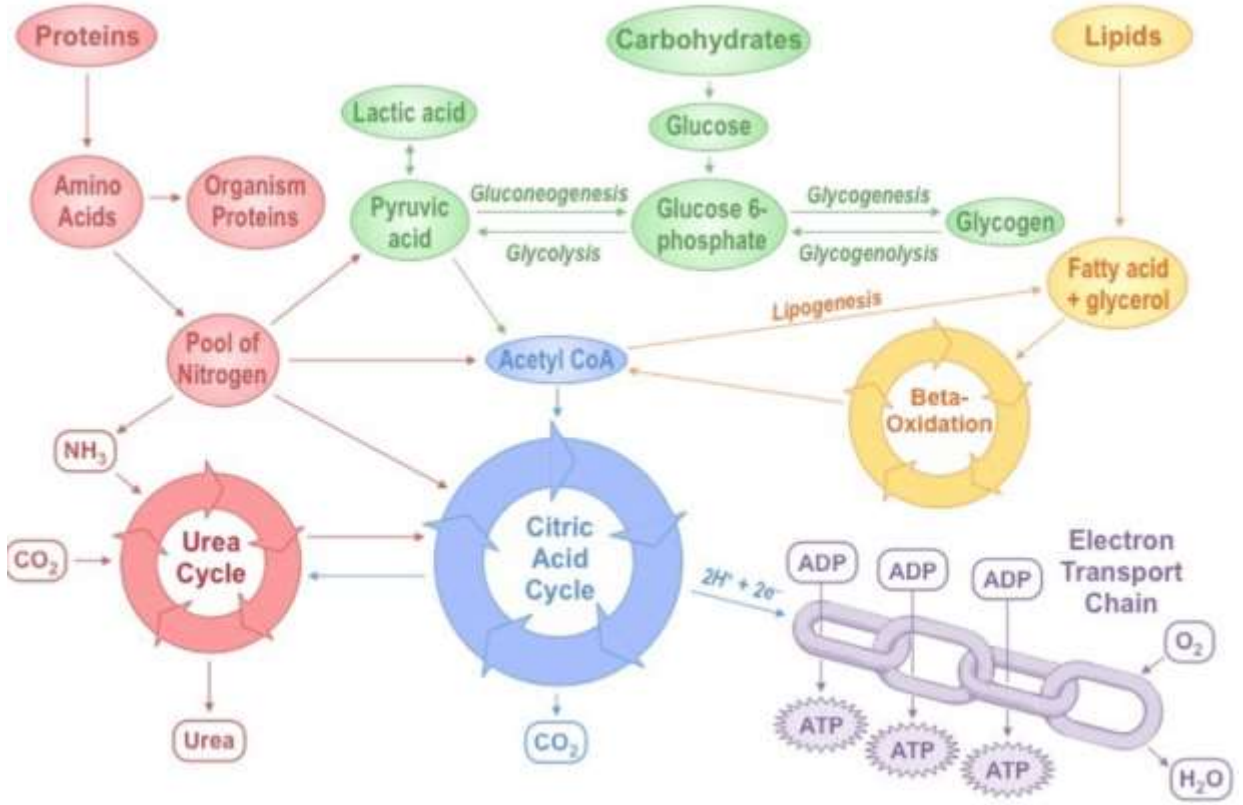
What happens to one unit of a given food?

Extremely complex

What happens to one unit of a given food?

In the next 20 mins, 20 hours, 20 days, 20 years

Extremely complex



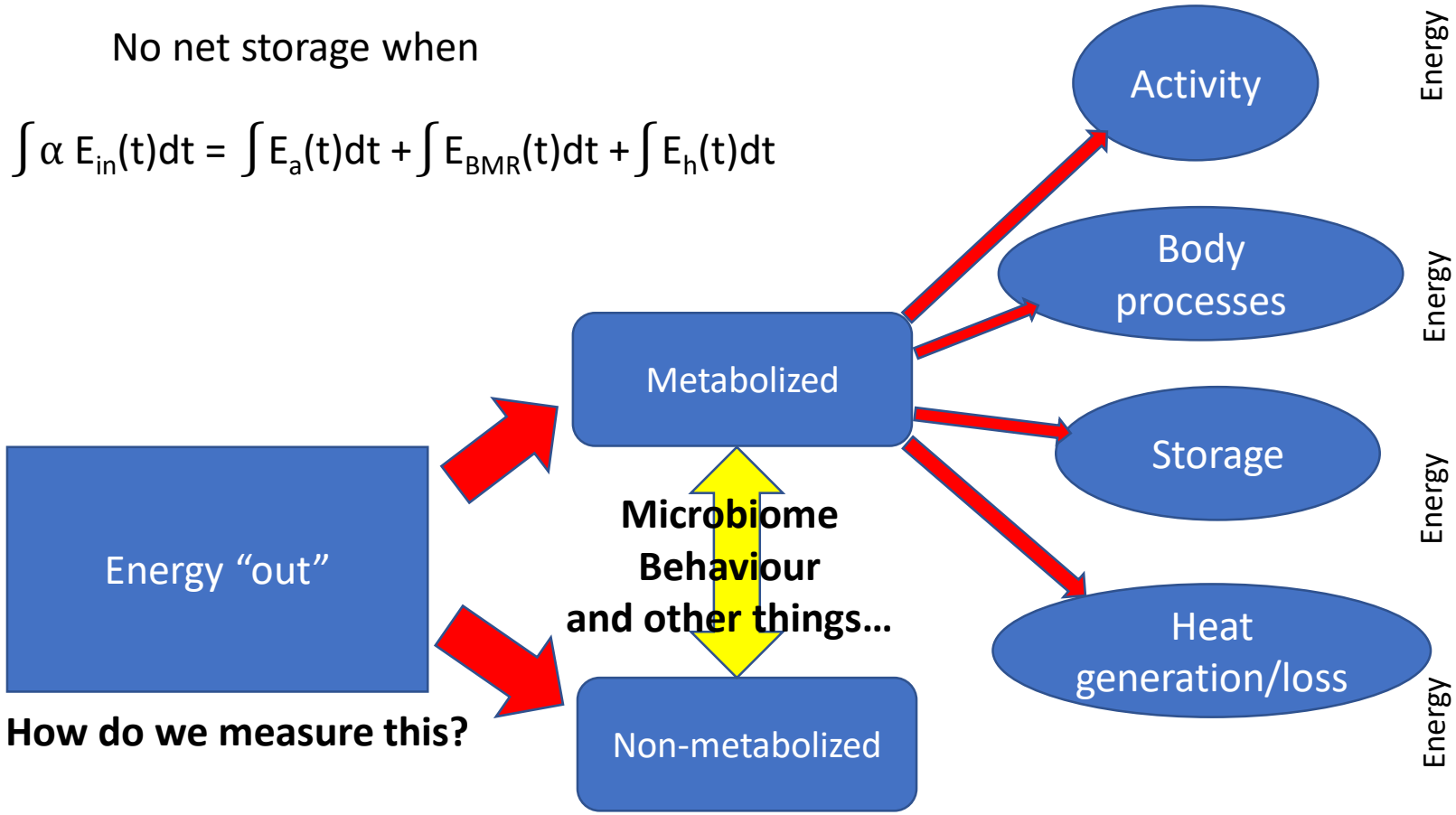
Everybody else is more expert than me

Back to Energy Conservation

$$\int \alpha E_{in}(t)dt = \int E_a(t)dt + \int E_{BMR}(t)dt + \int E_f(t)dt + \int E_h(t)dt$$

No net storage when

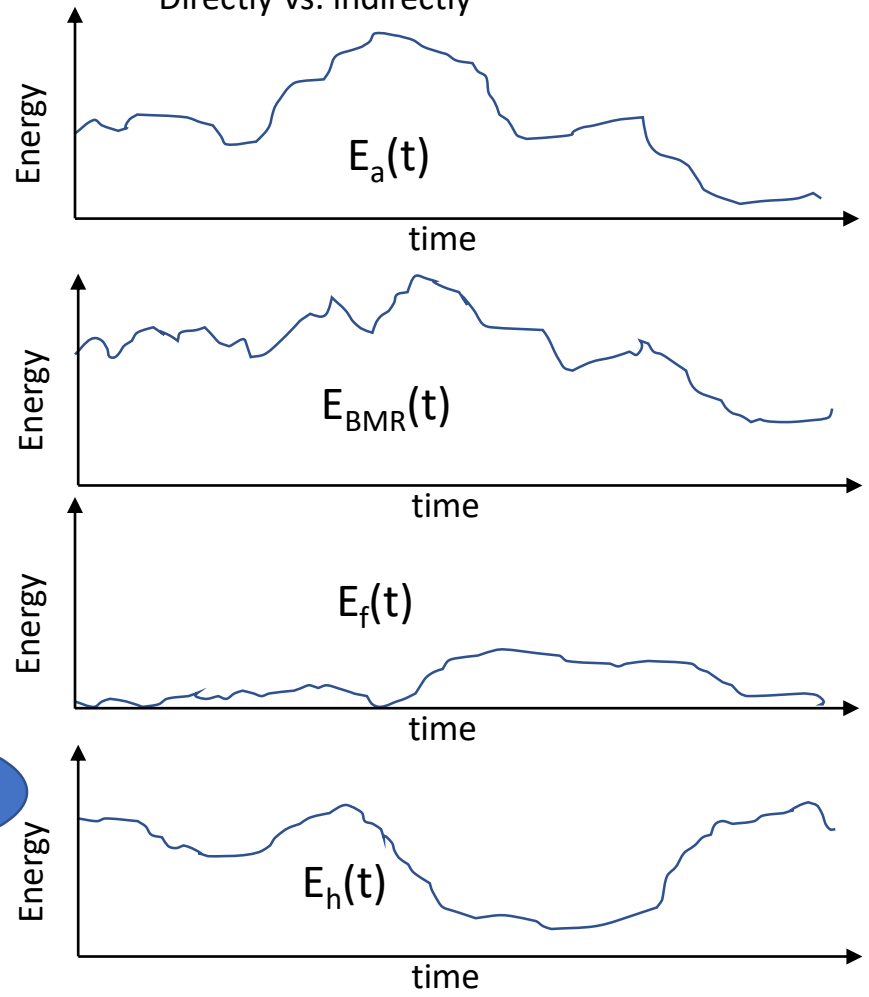
$$\int \alpha E_{in}(t)dt = \int E_a(t)dt + \int E_{BMR}(t)dt + \int E_h(t)dt$$



How do we measure this?

1) How do we measure these?

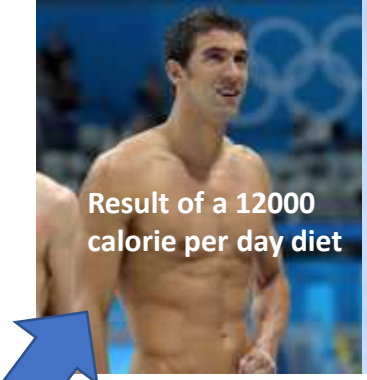
Directly vs. indirectly



2) How do they depend on behaviour?

3) How are they correlated in time?

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

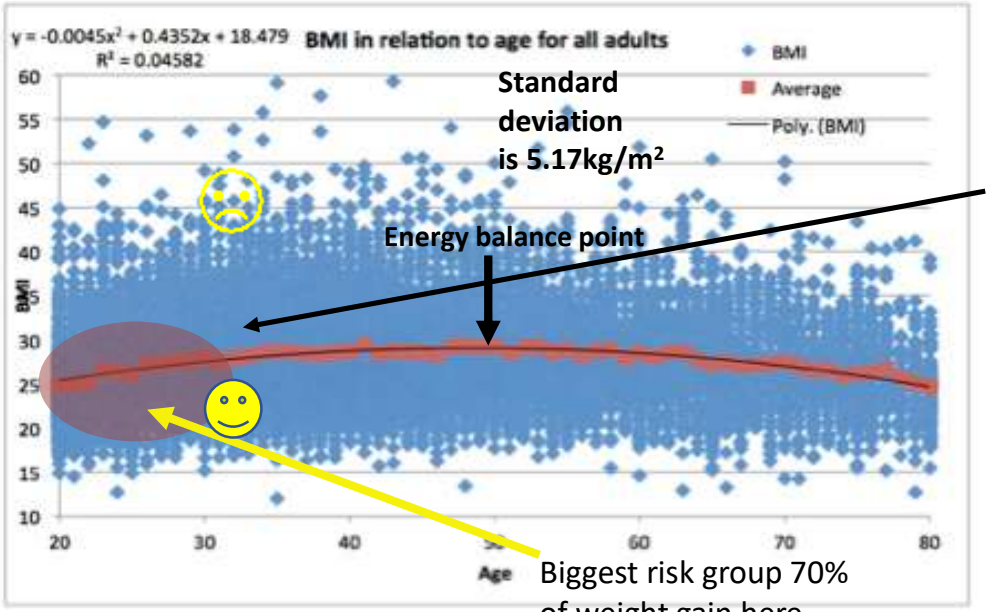
You can't gain weight without an associated set of decisions/actions that correspond to a behaviour

1. What are some of those behaviours?
2. How do we quantify/measure them?
3. What are risk factors for those behaviours?
4. How plastic are they?
5. How do we model them?

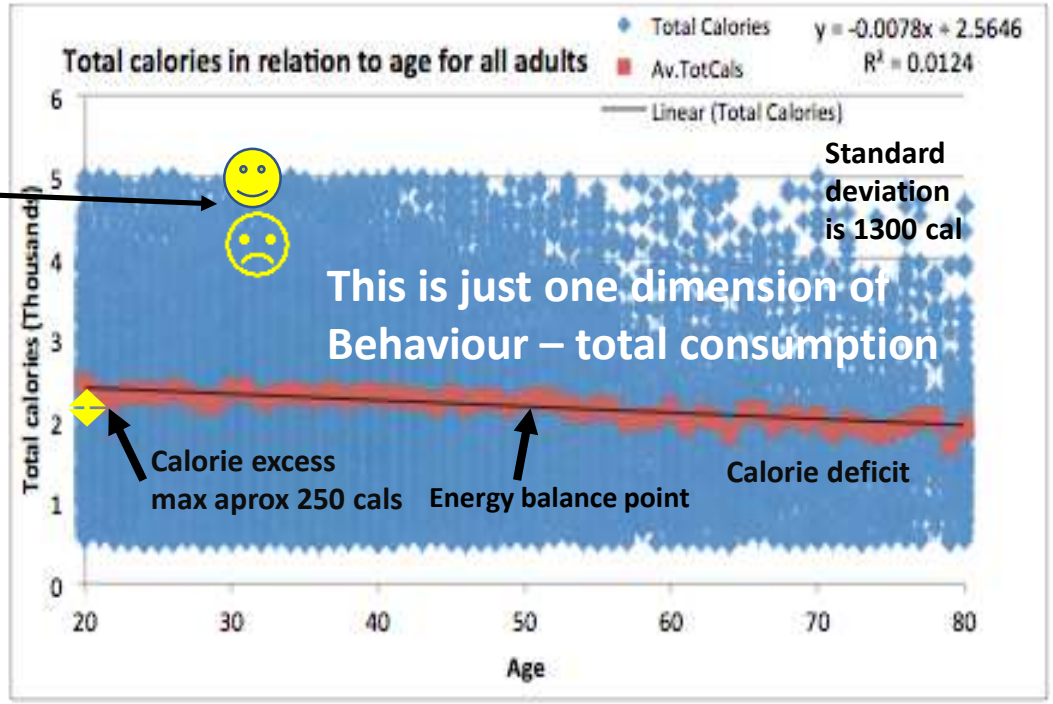
1) What are some of those behaviours?
Consumption and Exercise

2. Consumption...

You aren´t what you eat you become what you eat



This isn't noise its multifactoriality



Epidemiological data from ENSANUT 2006

Regression of BMI change versus calorie excess

	Variable(s)	Unstd. B	Std. Error	t	f	R^2	Sig	Lower	Upper
Moving Av.					29.236	0.343	0		
BMI Change	Constant	-1.954	0.362	-5.392			0	-2.68	-1.228
ALL	Total_Cals	0.904	0.167	5.407			0	0.569	1.239
	Variable(s)	Unstd. B	Std. Error	t	f	R^2	Sig	Lower	Upper
Moving Av.					13.397	0.193	0.001		
BMI Change	Constant	-1.625	0.444	-3.656			0.001	-2.515	-0.734
Men	Total_Cals	0.724	0.198	3.66			0.001	0.328	1.121
	Variable(s)	Unstd. B	Std. Error	t	f	R^2	Sig	Lower	Upper
Moving Av.					22.429	0.286	0		
BMI Change	Constant	-1.754	0.372	-4.711			0	-2.5	-1.008
Women	Total_Cals	0.833	0.176	4.736			0	0.481	1.185

This gradually decreasing calorie excess seems to be the motor for the population level increase in BMI

The Challenge of Measuring ”Real World” Energy Imbalance:
Some Phenomenological Observations

1) Population Energy Balance is a truly Emergent phenomenon

Why?

2) Maximum calorie excess is 250 cal but the population level std dev is 1300 cal

3) Calorie excess changes by only 8 calories per year

4) Average BMI increase per year is 0.15kg/m^2 (400g) but the population level std dev is 5.17kg/m^2

5) For an excess of 250 cal one expects a yearly increase of 13kg
Over a 30 year period the excess is over 1,000,000. Using the 3500 cal/pound rules this should correspond to an increase of 140kg!

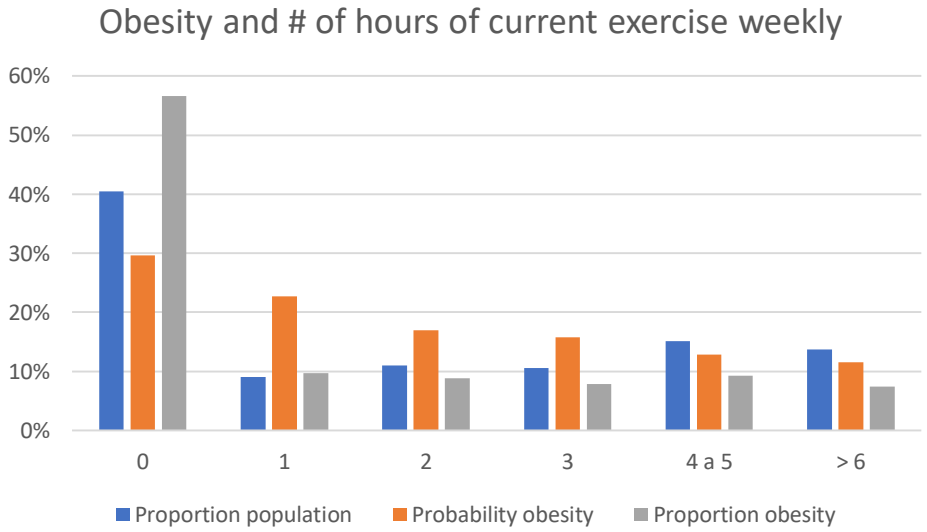
6) We should be even fatter! Where do all the calories go?

2. Exercise ...

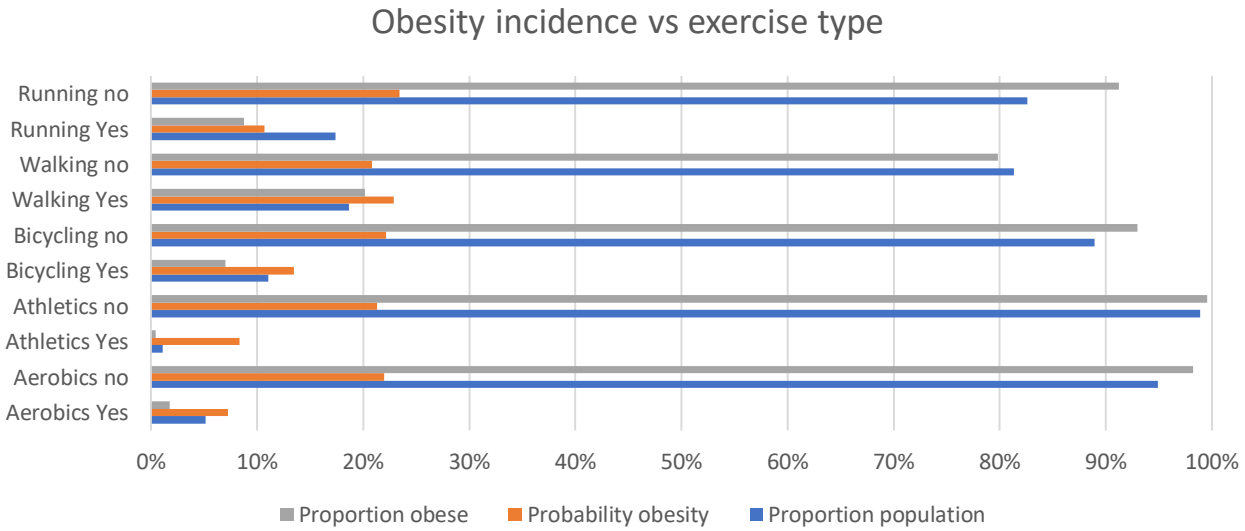
Obesity % versus historical exercise behavior
A > recommended exercise, B < recommended, * don't care;
(30y, 20y, 10y, 5y, 1y, now)

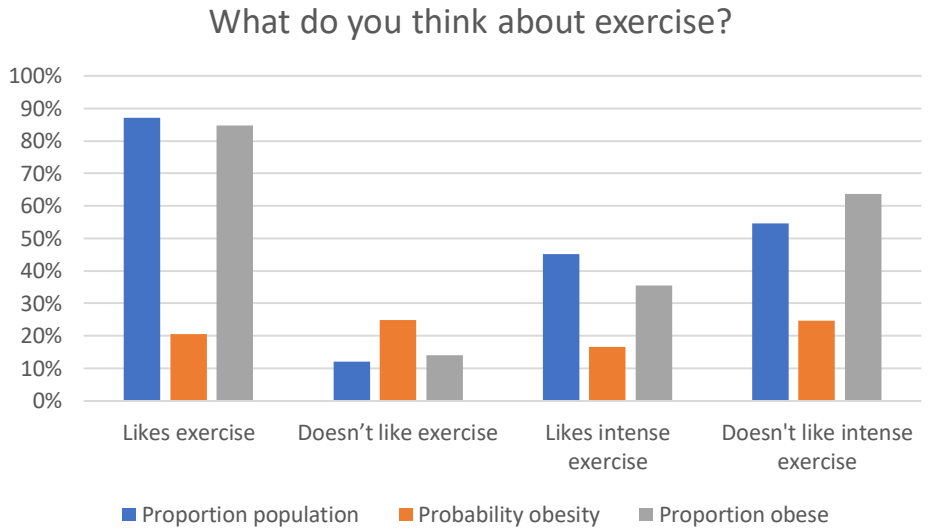
History	ϵ	N_x	N_{cx}	%	score
A*A*BB	3.56	94	38	40.43	0.73
AAA*B	3.55	91	37	40.66	0.74
AA**BB	3.53	113	44	38.94	0.67
AA**B*	3.40	131	49	37.40	0.60
A***BB	3.23	137	50	36.50	0.57
*A***A	-3.27	157	21	13.38	-0.75
**AAA	-3.27	157	21	13.38	-0.75
AA**AA	-3.51	103	10	9.71	-1.11
A**AA	-3.61	134	15	11.19	-0.95
***AA	-3.76	193	25	12.95	-0.79

Its worse to have had good habits and lost them than never to have had them

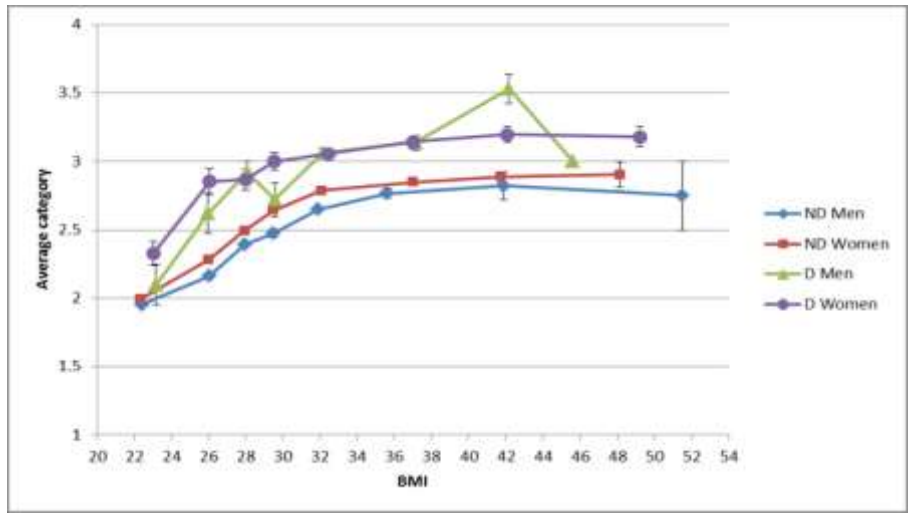


How many dimensions do we need to describe our decision making/actions and behavior with respect to exercise?





3. And some risk factors… being short, being non-academic, looking at the world through rose-tinted glasses,…

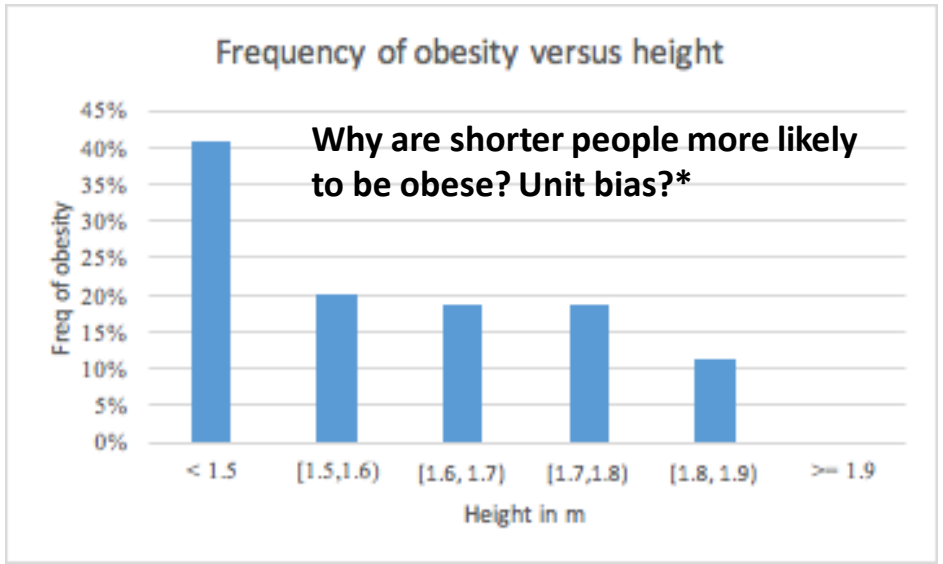


Probability to be an academic versus historical exercise behavior
A > recommended exercise, B < recommended, * don't care;
(30y, 20y, 10y, 5y, 1y, now)

History	ϵ	N_x	N_{cx}	%	score
*A***A	5.55	157	85	54.14	0.86
A**AA	5.21	134	73	54.48	0.88
AA**A	5.13	135	73	54.07	0.86
A*A*A	5.06	129	70	54.26	0.87
*A**A	4.97	165	85	51.52	0.76
*BBB**	-4.32	197	37	18.78	-0.77
**BB*	-4.40	267	55	20.60	-0.65
BBB	-4.41	207	39	18.84	-0.76
**BBB	-4.41	245	49	20.00	-0.69
**B*B	-4.55	260	52	20.00	-0.69

Effect of cognitive biases

- Self-serving
- Anchoring
- Unit



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

* Katherine Stephens

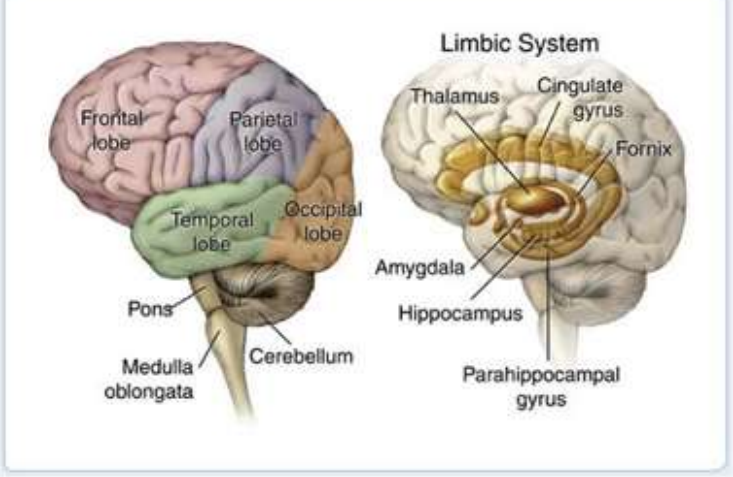
4. How plastic are they?

Estimates of Funding for Various Research, Condition, and Disease Categories NIH

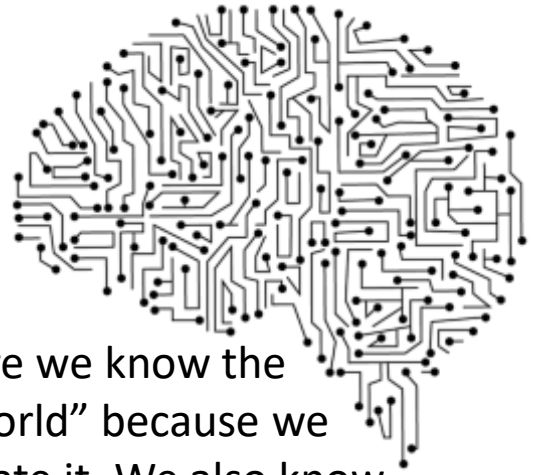
Research/Disease Areas	FY 2016Actual (Dollars in millions)	2015 US Mortality	2015 US Prevalence (Standard deviation)
Cancer	5589.00	652,672	8.7% (0.20%)
Cardiovascular	2108.00	1,464,485	-
Chronic Obstructive Pulmonary Disease	97.00	292,471	6.2% (0.18%)
Diabetes 4/	1084.00	252,806	9.7% (0.22%)
Digestive Diseases	1745.00	-	-
Heart Disease	1289.00	1,202,319	11.7% (0.26%)
Heart Disease - Coronary Heart Disease	419.00	536,339	6.1% (0.17%)
Hypertension	224.00	427,631	27.0% (0.33%)
Inflammatory Bowel Disease	126.00	2,966	-
Obesity	965.00	39,590	30.0% (0.38%)
Stroke	308.00	234,867	-
	13,954	5,106,146	
% of total	17%	73%	
Physical Activity	392.00	-	-
Prevention	7566.00	-	-
Tobacco	299.00	-	-
Nutrition	1615.00	-	-
Basic Behavioral and Social Science	1804.00	-	-
Behavioral and Social Science	4137.00	-	-
	15,813		

Not very! Well, at least not the healthy behaviors

5. How do we model them?



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



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

This…

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

Decision/Action **The “World”**

is the

CONDUCTOME

“World” + algorithm +payoff

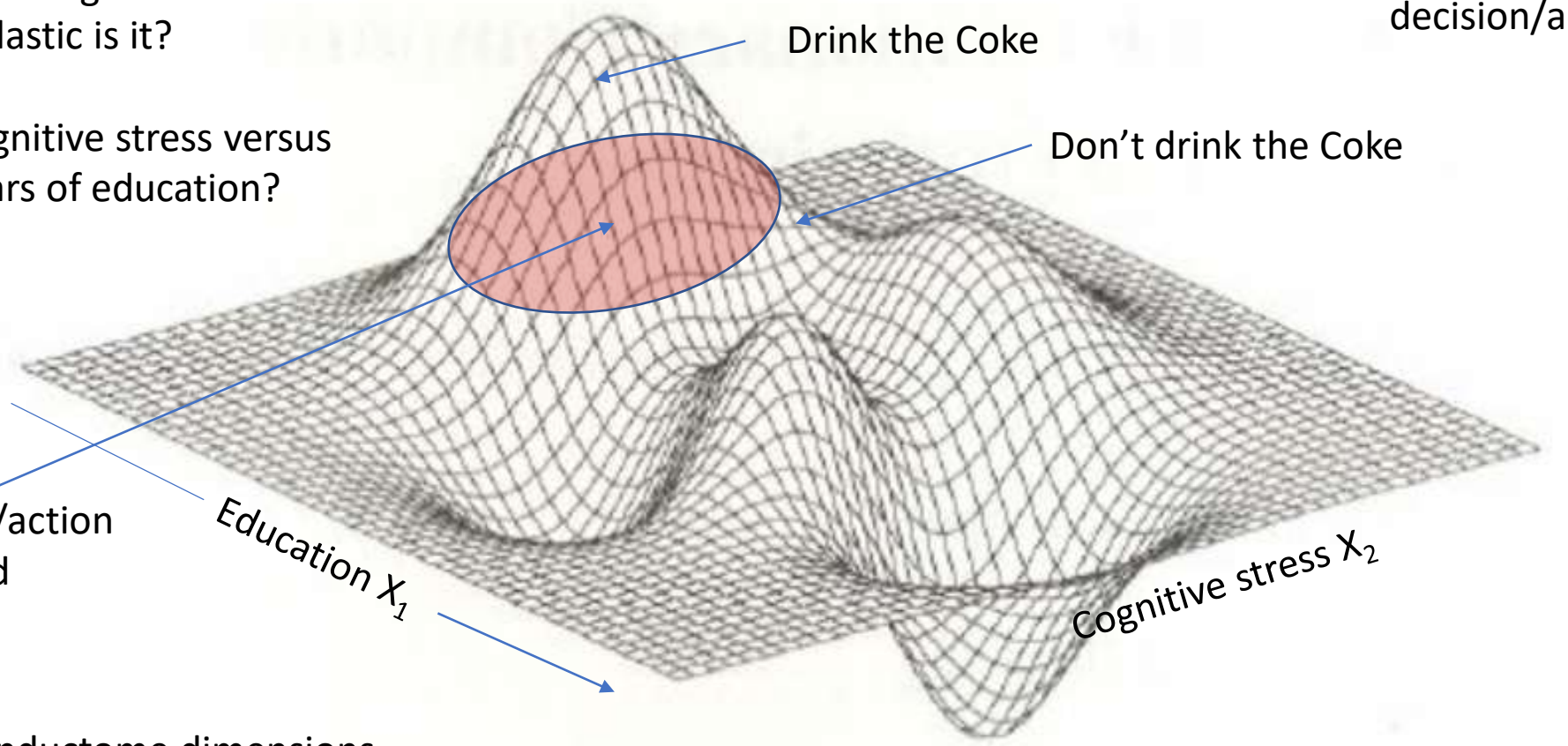
The Conductome also implicitly represents a Prediction Model where the prediction is that the decision/action will lead to some benefit.

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?

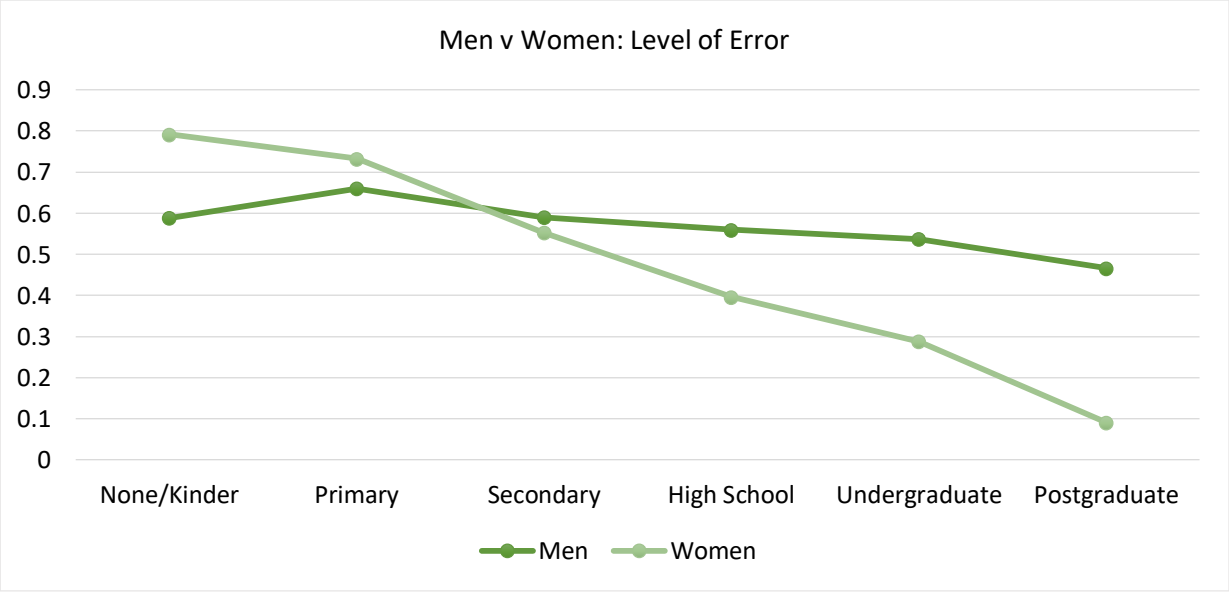
Reduce cognitive stress versus
5 more years of education?



(X_1, X_2) – Conductome dimensions

What does the Conductome represent?

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



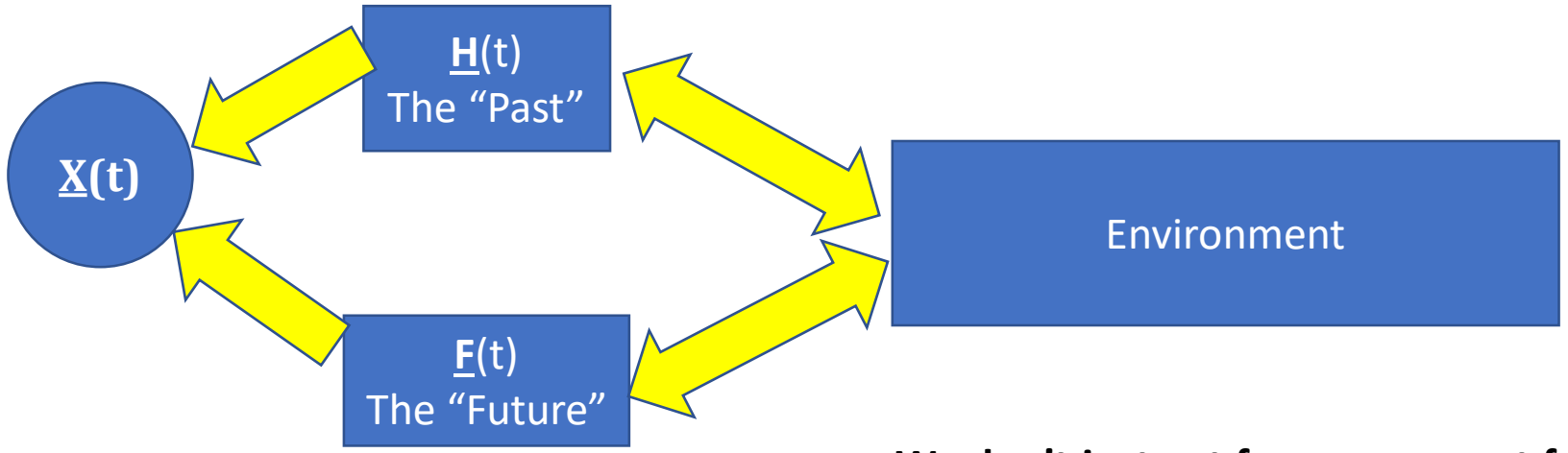
1) "In the last year have you lost or gained weight?"
2) "Was this weight loss intentional?"

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

Constructing the Conductome

What data? What algorithm? What payoff?

What data do we want? Rather, what data isn't potentially useful?
How should we organize the data part of the Conductome? Ontology and taxonomy.



We don't just eat for now, we eat for a predicted future
Our behavior is associated with that predicted future
But "who" does the prediction?
And how good is the prediction model?

Constructing the Conductome

First we need data

Goal: Construct the deepest data base on the planet (Deep Data, not Big Data) – to be publically available

Phase 0: National Epidemiological Surveys: ENSANUT 2006, 2012; ENCOPREVENIMSS

Phase I: (03-05/2014) 1,076 academicos and non-academicos from 12 institutes and faculties of the UNAM
2,524 variables - Genetic, epidemiological, physiological,… **Epidemiological**: Personal (81), Personal history (130), Family History (548), Self-health evaluation (226), Nutrition (220), Lifestyle (390), Health knowledge (293); **Genetic** (772); **Anthropometric and physiological** (49).

Phase II: (03/2017-09/2018) 500 medical students from the Fac. Med UNAM; (06/17) 100 workers and teachers from the FM. Addition of psychological variables.

Phase III: (12/2018-02/2019) 500 diabetics from the ISSTE

Phase IV: (01-03/2019) Follow up on 1,076 from Phase I. Repetition of blood analysis, addition of psychological variables, a new chip of approx. 700,000 SNPs (INMEGEN)

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

(CONACyT Fronteras 1093, CONACyT, Redes y PAPIIT, SECITI)

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
condi1	1	3.176688	41	17	1076	228	0.2119	0.4146	¿Cómo consideras tu condición física hace un año? 1 : Muy
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 : Regu
condi1	4	-2.65254	367	57	1076	228	0.2119	0.1553	¿Cómo consideras tu condición física hace un año? 4 : Buen

Epsilon	# participantes	# obesos	Proporcion obesos	Puesto
-2.81	234	32	13.68%	Academico
1.23	74	20	27.03%	Personal Admnistrativo
0.19	54	12	22.22%	Asistente
-1.64	10	0	0.00%	Coordinador
-2.38	52	4	7.69%	Estudiante
-3.58	81	4	4.94%	Estudiante Doctorado
-2.05	71	8	11.27%	Estudiante Maestria
2.03	110	32	29.09%	Intendencia
-0.53	85	16	18.82%	Investigador
0.51	3	1	33.33%	Investigador Emerito
2.41	96	30	31.25%	Jefe de Area
2.06	48	16	33.33%	Laborat
3.53	67	26	38.81%	Secreta
0.30	57	13	22.81%	Técnico
2.85	34	14	41.18%	Vigilant

Epsilon	# participantes	# obesos	Proporcion obesos	Edad
-4.18	122	7	5.74%	19 - 27
-2.79	145	17	11.72%	28 - 32
0.16	138	30	21.74%	33 - 37
2.30	133	39	29.32%	38 - 42
1.88	137	38	27.74%	43 - 47
			26.56%	48 - 52
			26.87%	53 - 58
			19.42%	59 - 81

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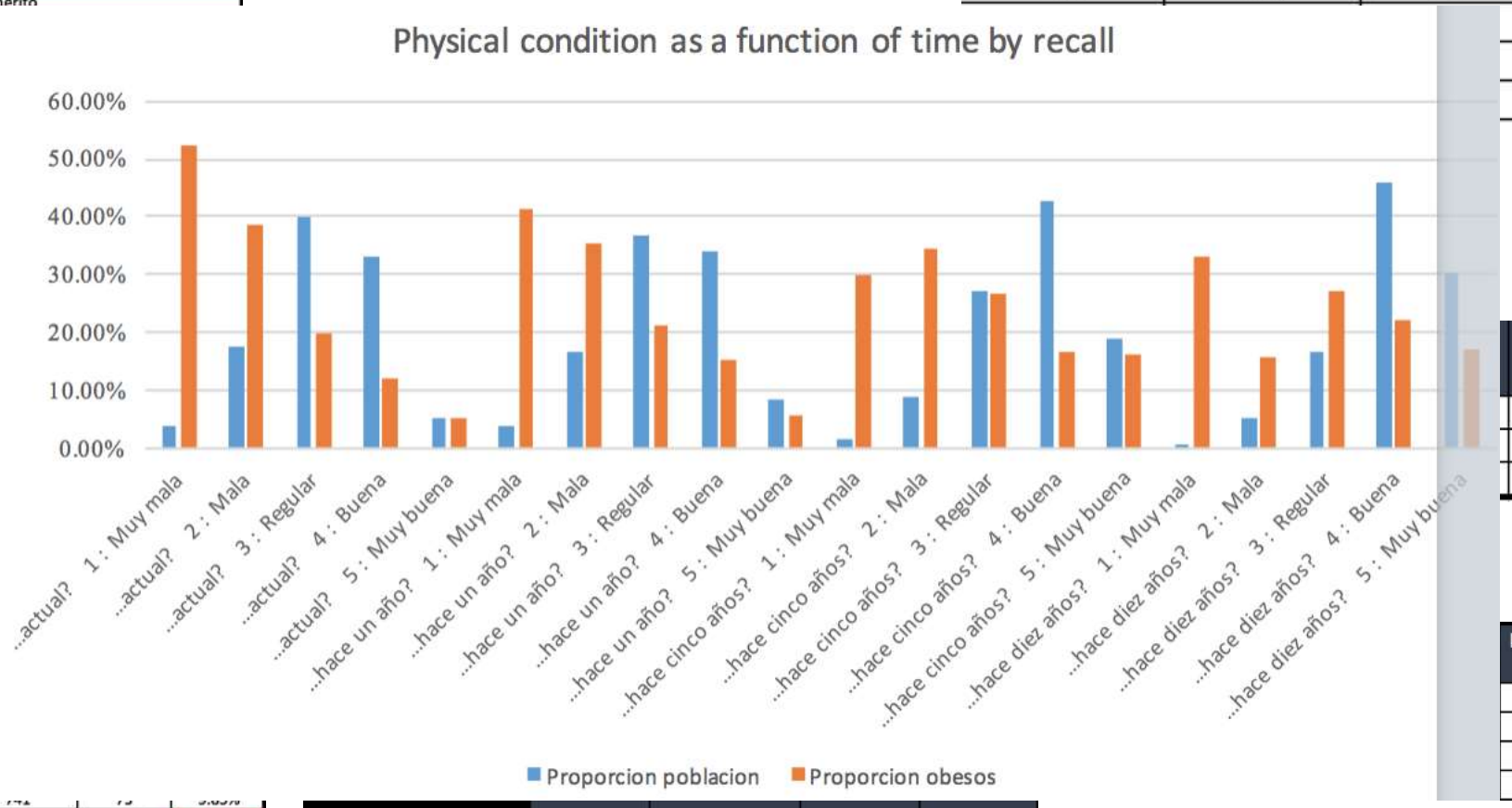


Proporcion obesos
31.18%
31.08%
19.38%

Enfermedad	Epsilon	# pa
No le han diagnosticado asma	-0.03	
Le han dignosticado asma	0.14	
No le han diag		
Le han diagnos		
No le han diag		
Le han diagnos		
No le han diag		
Le han diagnos		
No le han diag		

¿Cómo consideras tu peso actual?	Epsilon
Muy malo	-1.47
Malo	-3.70
Regular	-9.66
Bueno	4.65
Muy bueno	13.97

Le han diagnosticado otra enfermedad	0.08			
No le han diagnosticado cancer de prostata	-0.01			
Le han diagnosticado cancer de prostata	0.19			
No sabe si le han diagnosticado diabetes	-0.55			
Le han diagnosticado diabetes	2.72			
No le han diagnosticado hipertensión	-2.46			
Le han diagnosticado hipertensión	6.54			
No le han diagnosticado problemas neuronales	0.00			
Le han diagnosticado problemas neuronales	-0.01			
No sabe si le han diagnosticado obesidad	-7.55			
Le han diagnosticado obesidad	11.32	333	155	46.55%
No sabe si le han diagnosticado prediabetes	-0.42	993	205	20.64%
Le han diagnosticado prediabetes	1.72	79	23	29.11%
No le han diagnosticado problemas pulmonares	-0.30	1057	220	20.81%
Le han diagnosticado problemas pulmonares	2.23	19	8	42.11%
No le han diagnosticado problemas renales	-0.13	1065	224	21.03%
Le han diagnosticado problemas renales	1.23	11	4	36.36%
No le han diagnosticado problemas de retinopatia	0.05	1059	225	21.25%
Le han dignosticado problemas de retinopatia	-0.36	17	3	17.65%
No le han diagnosticado trigliceridos altos	-0.84	772	154	19.95%
Le han diagnosticado trigliceridos altos	1.35	304	74	24.34%

¿Cómo consideras que es tu salud actualmente?	Epsilon	# participantes	# obesos	Proporcion obesos
1 : Muy mala	1.15	15	5	33.33%
2 : Mala	5.15	60	29	48.33%
3 : Regular	4.41	366	112	30.60%
4 : Buena	-3.76	536	78	14.55%
5 : Muy buena	-4.30	95	3	3.16%

Probabilidad obesidad	Proporcion obesos
28.92%	97.81%
1.26%	1.32%
3.17%	0.88%
0.00%	0.00%

Relevence of genetics

Driver	Value	Epsilon	P(C/X)	P(C)	N(X/C)	N(X)	N(C)	NTotal
rs2943641_A	2	2.9391	0.6000	0.2169	6	10	123	567
rs2972146_C	2	2.9391	0.6000	0.2169	6	10	123	567
rs2943650_G	2	2.9391	0.6000	0.2169	6	10	123	567
rs12629908_A	2	2.6981	0.3116	0.2169	43	138	123	567
rs870347_C	2	2.2200	0.2914	0.2169	44	151	123	567
rs1407434_G	0	2.1617	0.2841	0.2169	50	176	123	567
rs972283_A	2	2.1543	0.3085	0.2169	29	94	123	567
rs10496971_C	2	1.9688	0.3011	0.2169	28	93	123	567
rs2241766_C	1	1.9472	0.2741	0.2169	54	197	123	567
rs10885122_A	2	1.9426	0.5000	0.2169	4	8	123	567
rs2986742_G	2	1.9121	0.4545	0.2169	5	11	123	567
rs1799884_A	2	-2.0385	0.0000	0.2169	0	15	123	567
rs3943253_A	2	-2.0502	0.1364	0.2169	15	110	123	567
rs4607517_A	2	-2.1053	0.0000	0.2169	0	16	123	567
rs4880436_A	2	-2.1388	0.0870	0.2169	4	46	123	567
rs174537_C	2	-2.1927	0.0851	0.2169	4	47	123	567
rs174546_G	2	-2.1927	0.0851	0.2169	4	47	123	567
rs174550_A	2	-2.1927	0.0851	0.2169	4	47	123	567
rs972283_A	0	-2.3181	0.1521	0.2169	33	217	123	567
rs2073821_A	2	-2.3502	0.1170	0.2169	11	94	123	567
rs1513181_G	2	-2.3605	0.1250	0.2169	14	112	123	567
rs2237895_A	2	-2.3836	0.1308	0.2169	17	130	123	567
rs7803075_G	2	-2.4635	0.0847	0.2169	5	59	123	567
rs896854_A	0	-2.5528	0.1398	0.2169	26	186	123	567
rs7809589_C	2	-2.5964	0.1231	0.2169	16	130	123	567
rs1111875_A	0	-3.2065	0.1211	0.2169	23	190	123	567

Project UNAM: Genetic analysis of 568 participants

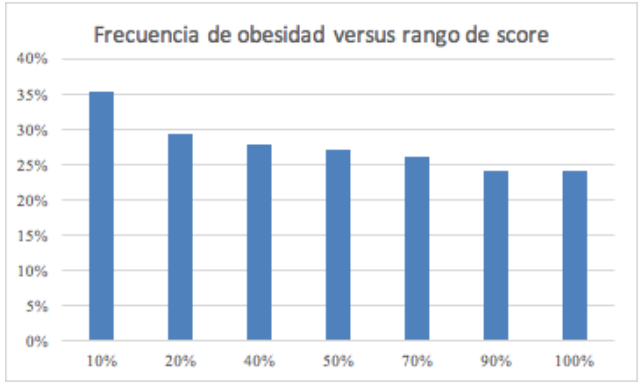
347 SNPs considered - Subsets with obesity, DM2, dislipidemias, hepatic; Collaboration with Dr. Samuel Canizales UNAM/INMEGEN

obesity (score = 0.904, predictive but rare)

obesity (score = 0.105, not so predictive but common)

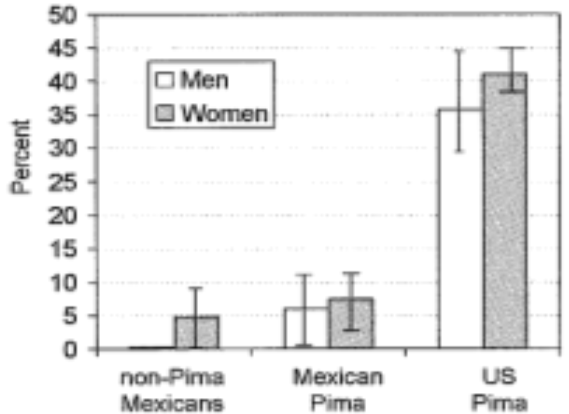
Where is the ”thrifty gene”?

What is the genetics of conduct?



The model doesn’t offer much predictability

consistent with:



Conclusions and questions

- Why can’t we revert the obesity crisis at a large scale? We need new paradigms. Hopefully the Conductome can be useful.
- The Conductome is enormously multifactorial, it requires big, deep data at multiple scales: genetic, epigenetic, physiologcal, psychological, neurosciencies, epidemiology, sociology, economics,…
  - We don’t have them.
- The Conductome requires adequate frameworks for the generation and sharing of data
  - We don’t have them.
- The Conductome requires truly interdisciplinary teams to analyse and model these data
  - We don’t have them.
- The Conductome requires new frameworks capable of modelling Complex Adaptive Systems
  - We don’t have them.
- The Conductome implies that we have to look at science in a different way; how we do it and how we present it - the challenge of multifactoriality
- Hopefully in this meeting we can make some progress.

Questions

1. What is the appropriate taxonomy of those "universal" tendencies in human physiology/ behaviour that are associated with the obesity pandemic?
2. What are the genetic/ epigenetic underpinnings of these "universal" tendencies?
3. What are the phenotypic variables that will most help to identify these tendencies? (Stop looking for only high signal to noise relations)
4. How have the consequences of those tendencies changed due to environmental changes (and how has the environment objectively changed?)
5. How do we quantify the effect of a given variable/ class of variables?
6. What is the impact of time horizon on a given variable (e.g., the difference between being obese for one year versus 20)
7. How do we disentangle the cause-effect relationships?
8. What is actionable? What factors are plastic and what is their degree of plasticity?