

Cardiac Systems Biology

in

Drosophila melanogaster

- Metabolomics of Hypoxia
- Molecular Algorithms and Cardiac Aging

Metabolomics of Hypoxia

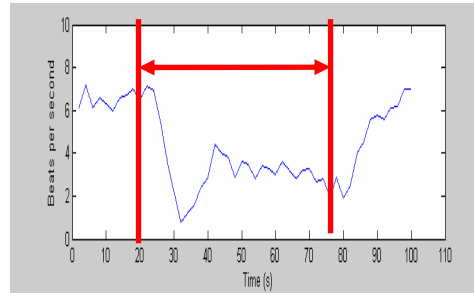
Jake Feala

Laurence Coquin

Andrew McCulloch

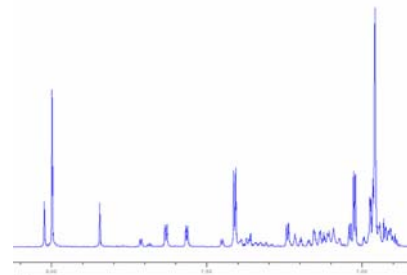
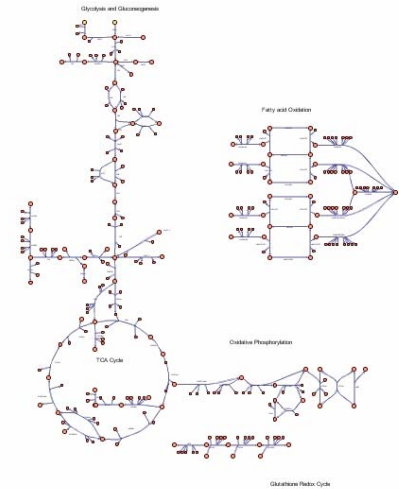
Energy Metabolism in Hypoxic Myocardium

Experiment



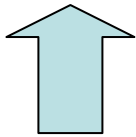
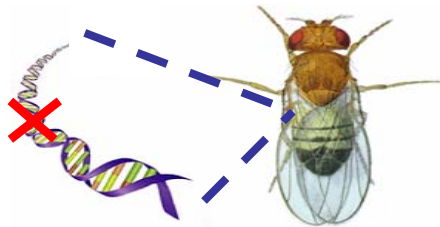
cardiac phenotype

Model



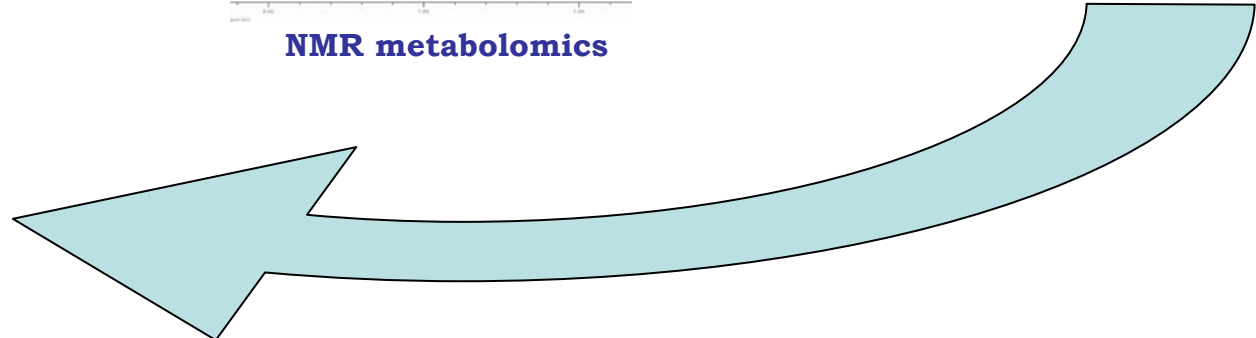
NMR metabolomics

Genetic perturbation



Accession Name	Gene Symbol	Pubmed ID	Cardiac Role
Fggn00000000	CG17028		unknown
Fggn00000004	Pu1		border cell
Fggn00000018	CG13773	PCO1, and	
Fggn00000020	CG14688		
Fggn00000021	CG14617		
Fggn00000024	CG11878A		cardiac
Fggn00000028	CG14618		
Fggn00000031	CG14619		
Fggn00000032	CG14620		
Fggn00000033	CG14621		
Fggn00000034	CG14622		
Fggn00000035	CG14623		
Fggn00000036	CG14624		
Fggn00000037	CG14625		
Fggn00000038	CG14626		
Fggn00000039	CG14627		
Fggn00000040	CG14628		
Fggn00000041	CG14629		
Fggn00000042	CG14630		
Fggn00000043	CG14631		
Fggn00000044	CG14632		
Fggn00000045	CG14633		
Fggn00000046	CG14634		
Fggn00000047	CG14635		
Fggn00000048	CG14636		
Fggn00000049	CG14637		
Fggn00000050	CG14638		
Fggn00000051	CG14639		
Fggn00000052	CG14640		
Fggn00000053	CG14641		
Fggn00000054	CG14642		
Fggn00000055	CG14643		
Fggn00000056	CG14644		
Fggn00000057	CG14645		
Fggn00000058	CG14646		
Fggn00000059	CG14647		
Fggn00000060	CG14648		
Fggn00000061	CG14649		
Fggn00000062	CG14650		
Fggn00000063	CG14651		
Fggn00000064	CG14652		
Fggn00000065	CG14653		
Fggn00000066	CG14654		
Fggn00000067	CG14655		
Fggn00000068	CG14656		
Fggn00000069	CG14657		
Fggn00000070	CG14658		
Fggn00000071	CG14659		
Fggn00000072	CG14660		
Fggn00000073	CG14661		
Fggn00000074	CG14662		
Fggn00000075	CG14663		
Fggn00000076	CG14664		
Fggn00000077	CG14665		
Fggn00000078	CG14666		
Fggn00000079	CG14667		
Fggn00000080	CG14668		
Fggn00000081	CG14669		
Fggn00000082	CG14670		
Fggn00000083	CG14671		
Fggn00000084	CG14672		
Fggn00000085	CG14673		
Fggn00000086	CG14674		
Fggn00000087	CG14675		
Fggn00000088	CG14676		
Fggn00000089	CG14677		
Fggn00000090	CG14678		
Fggn00000091	CG14679		
Fggn00000092	CG14680		
Fggn00000093	CG14681		
Fggn00000094	CG14682		
Fggn00000095	CG14683		
Fggn00000096	CG14684		
Fggn00000097	CG14685		
Fggn00000098	CG14686		
Fggn00000099	CG14687		
Fggn00000100	CG14688		

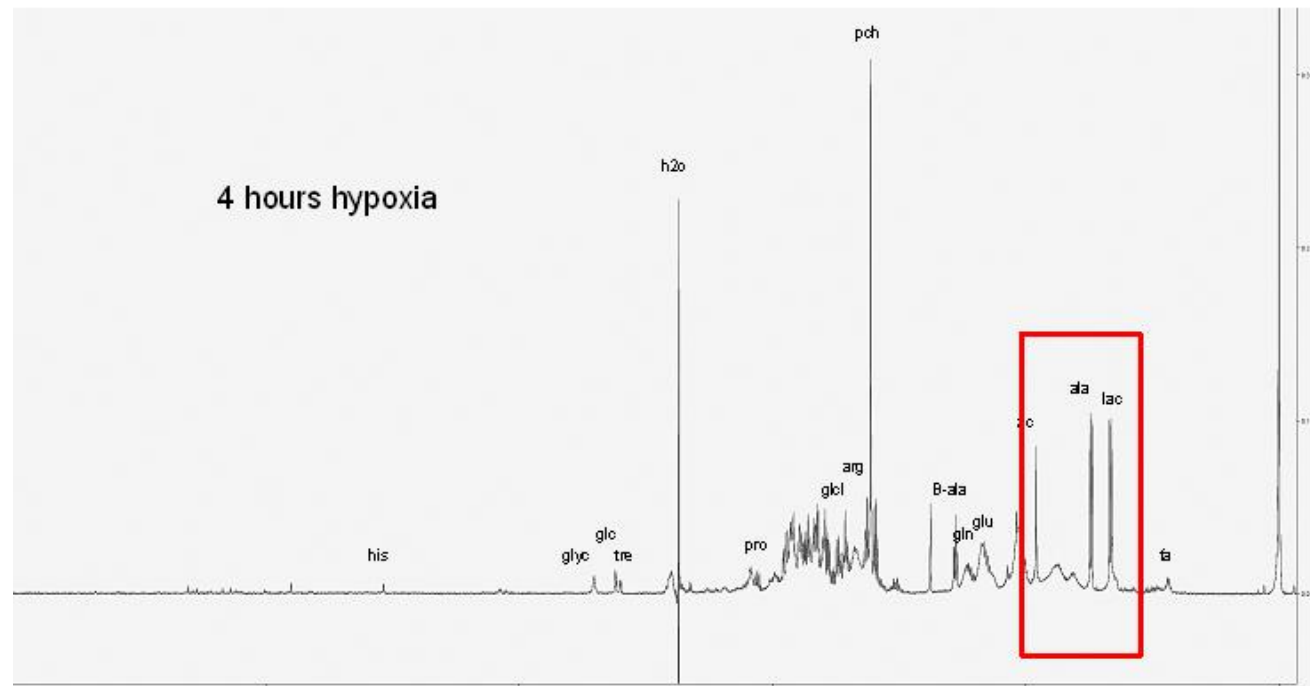
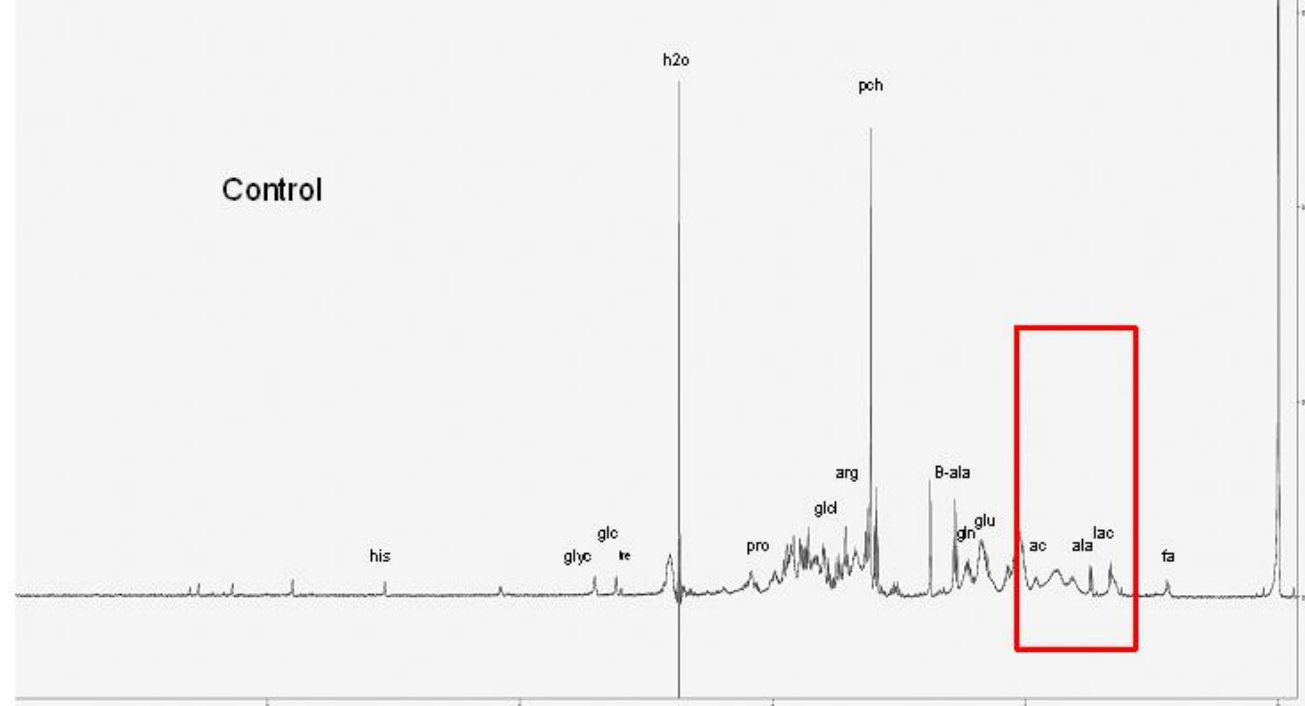
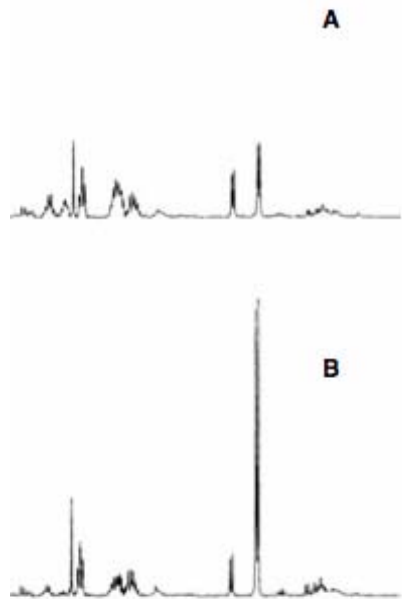
Candidate genes



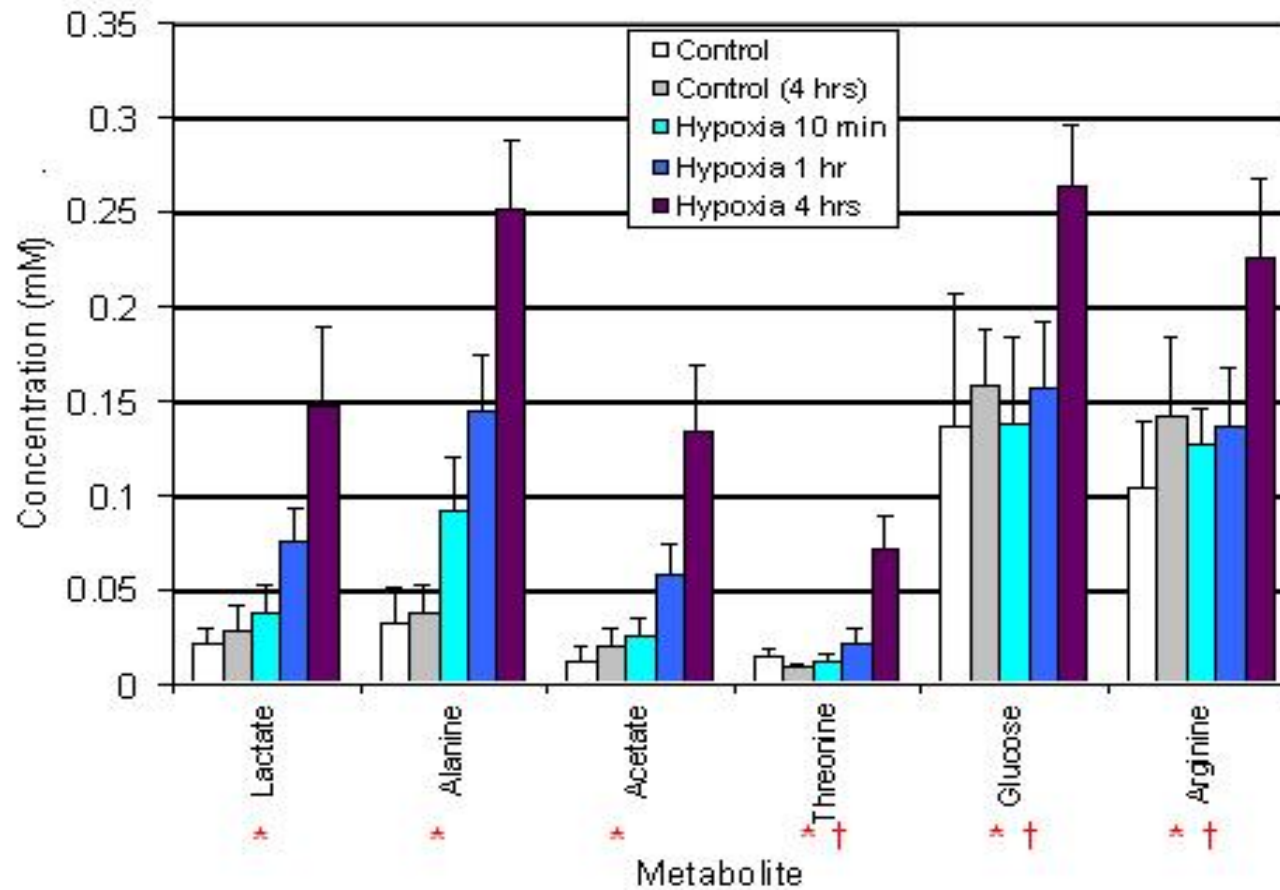
^1H NMR spectroscopy of hypoxic fly muscle

- 0.5% O_2
- 240 minutes

MAMMALIAN TISSUE:



Metabolites affected by hypoxia



Reconstructing the metabolic network in *Drosophila*

- 162 genes, 143 proteins and 158 reactions
- Includes glycolysis, TCA cycle, oxidative phosphorylation, Beta-oxidation, amino acids
- Elementally- and charge-balanced

Metabolic network reconstruction

Literature and Databases



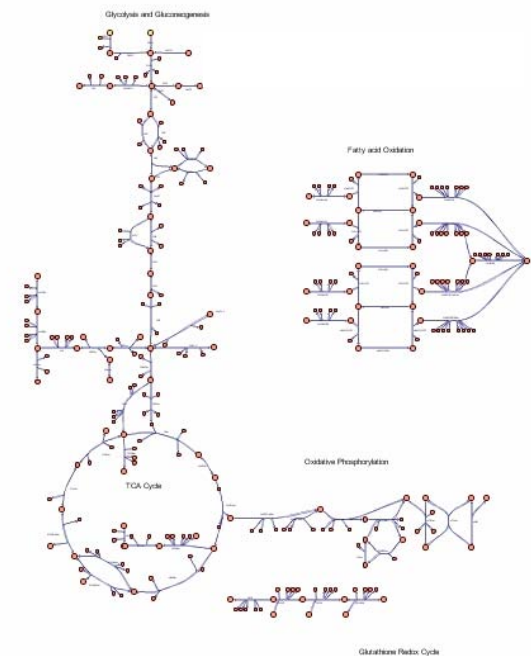
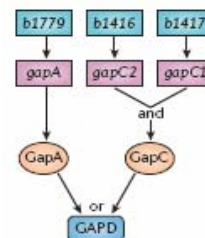
Annotated Genome FlyBase

Stoichiometric matrix

ATP	-1	0	-1	0
GLC	-1	0	0	0
ADP	1	0	1	0
G6P	1	-1	0	0
H	1	0	1	0
F6P	0	1	-1	0
FDP	0	0	1	-1
DHAP	0	0	0	1
G3P	0	0	0	1
H ₂ O	0	0	0	0
PYR	0	0	0	0
	HEX1	PGI	PFK	FBA

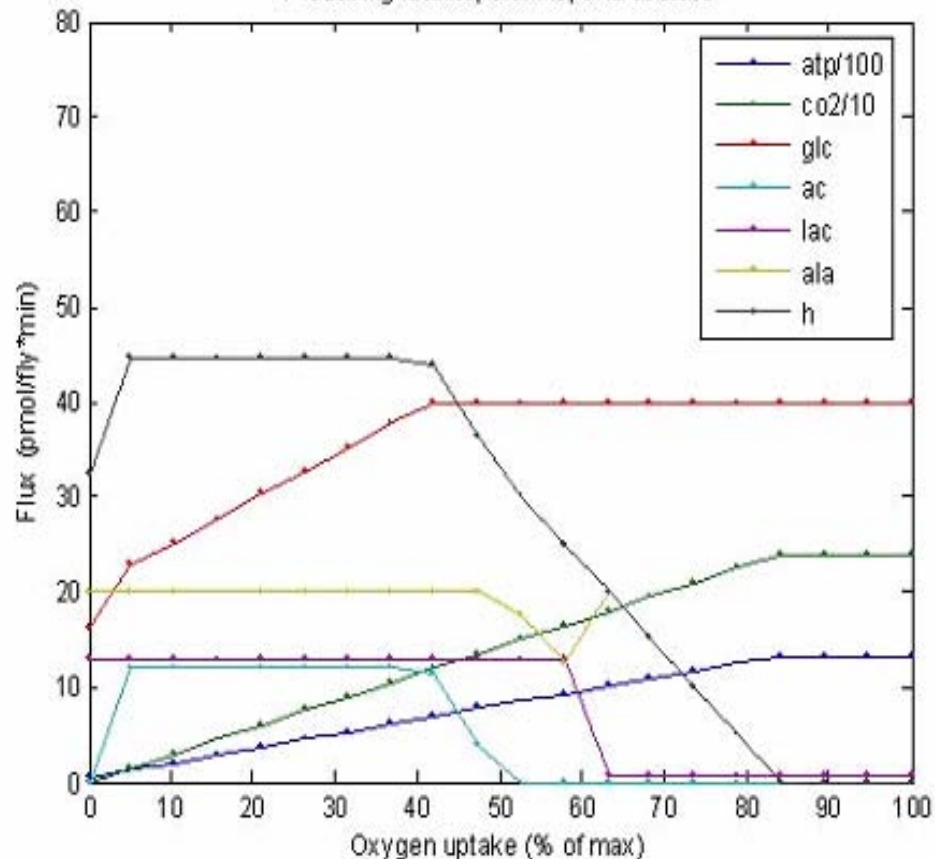


Gene-protein-reaction associations

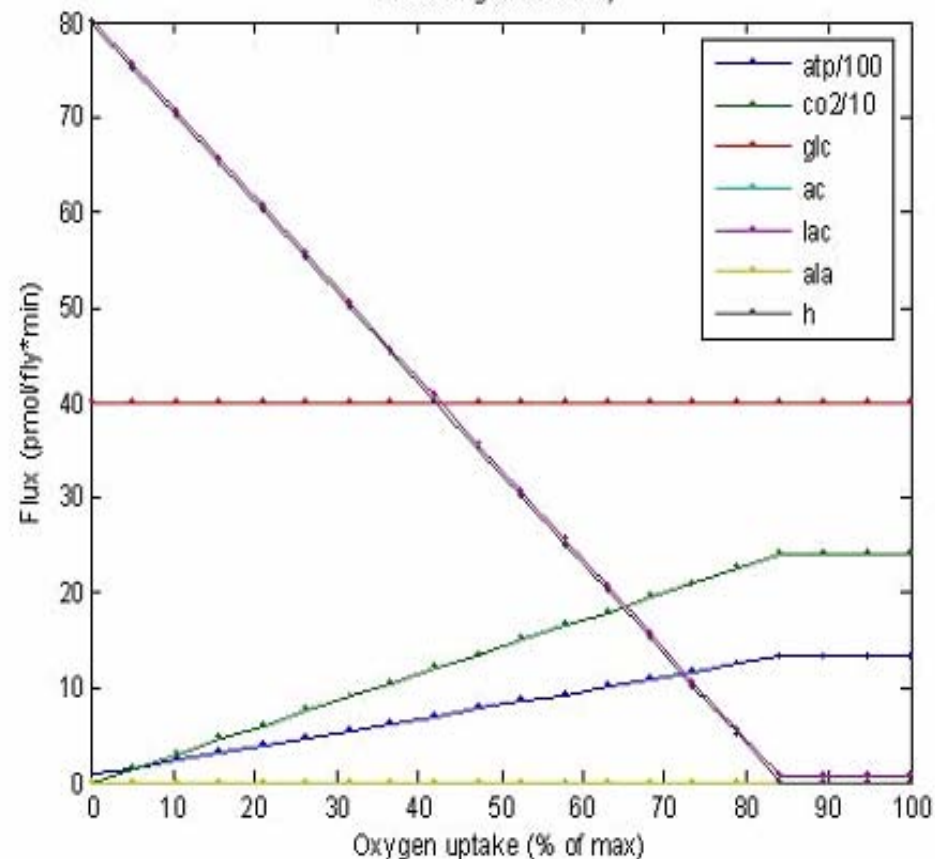


Substrates and products during hypoxia

Producing lactate, alanine, and acetate

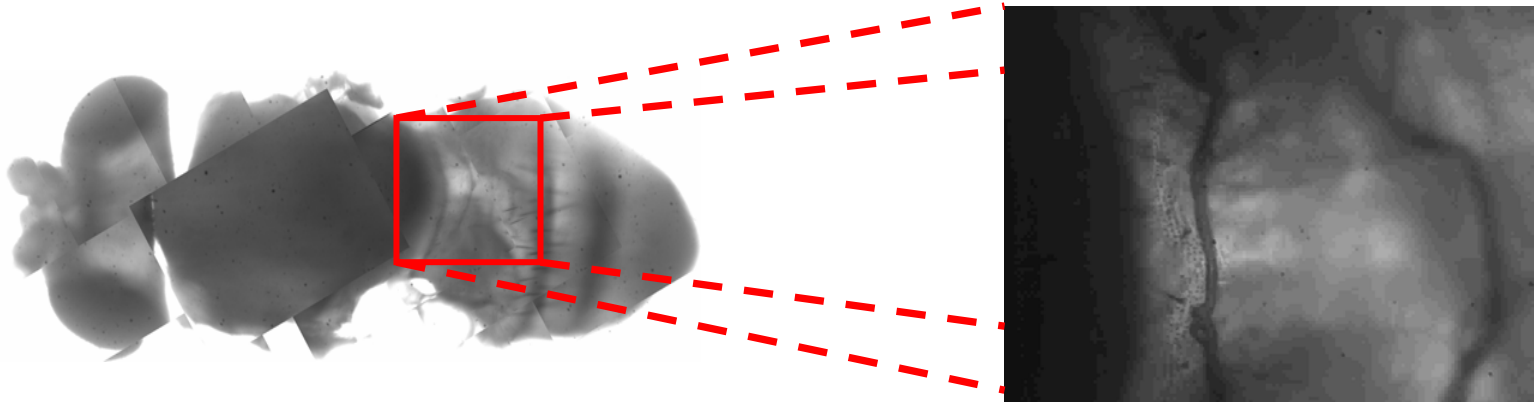
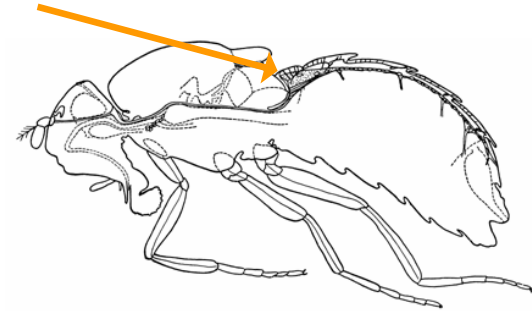
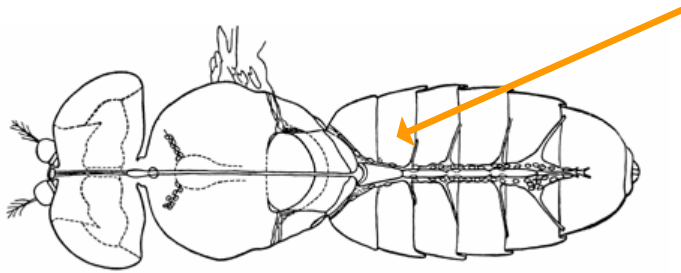


Producing lactate only

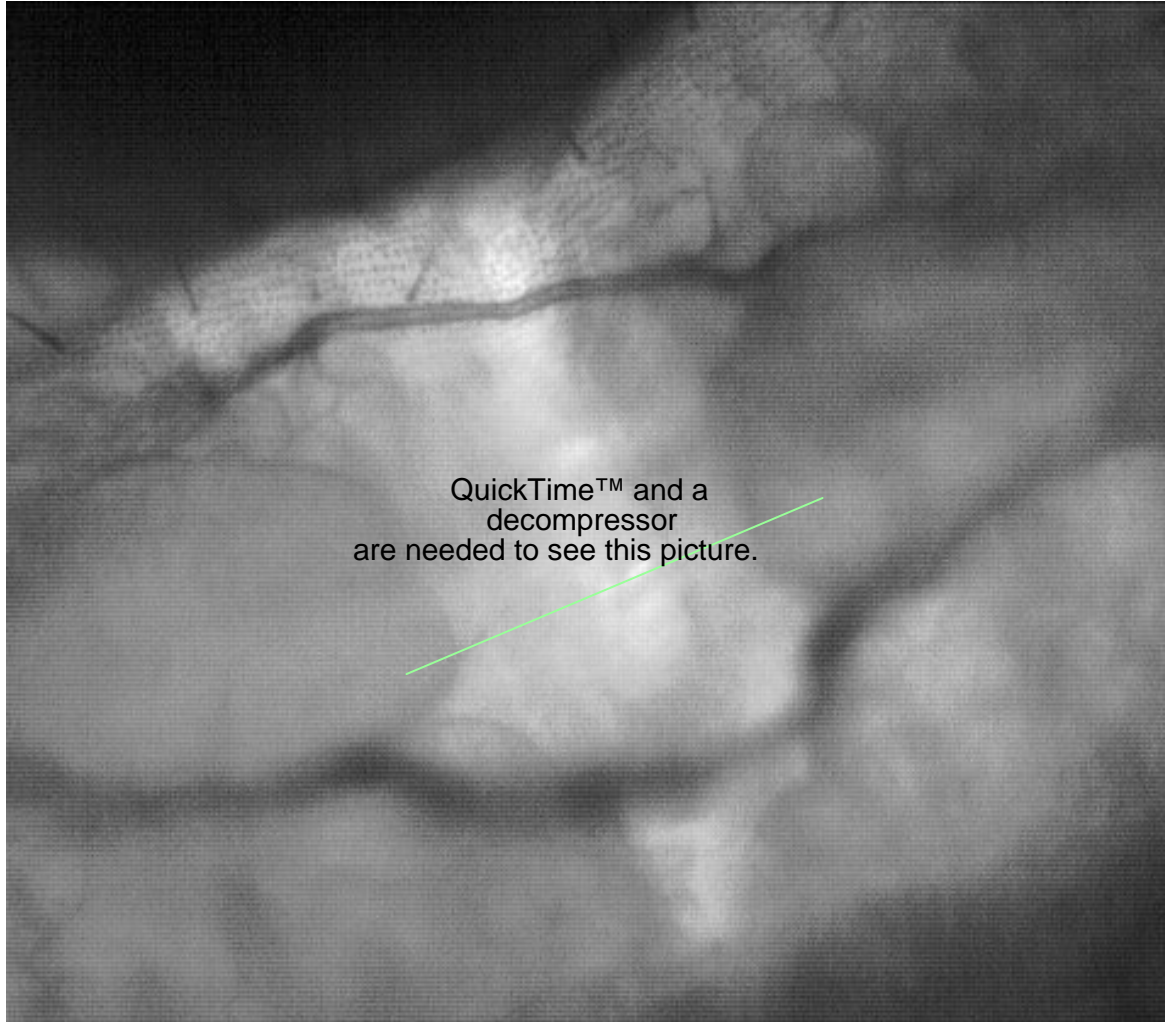


- h: proton production

The fly heart

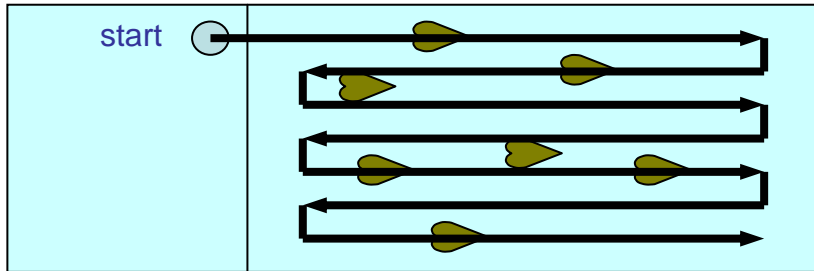


Fruit Fly Heart

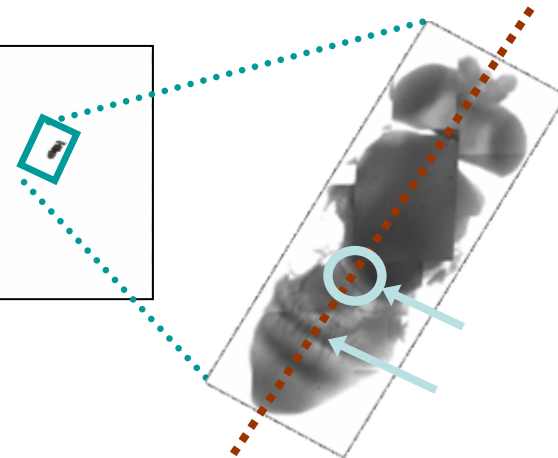
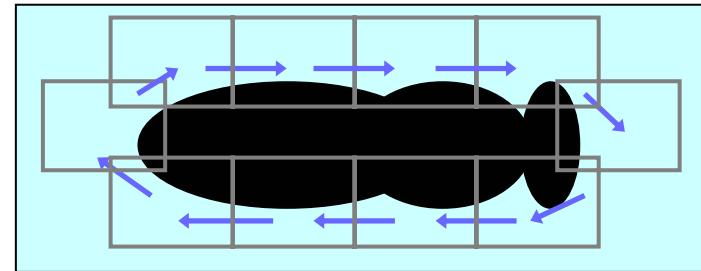


High-throughput measurements of heart function in *Drosophila*

1 Scan



2 Trace



Molecular Algorithms

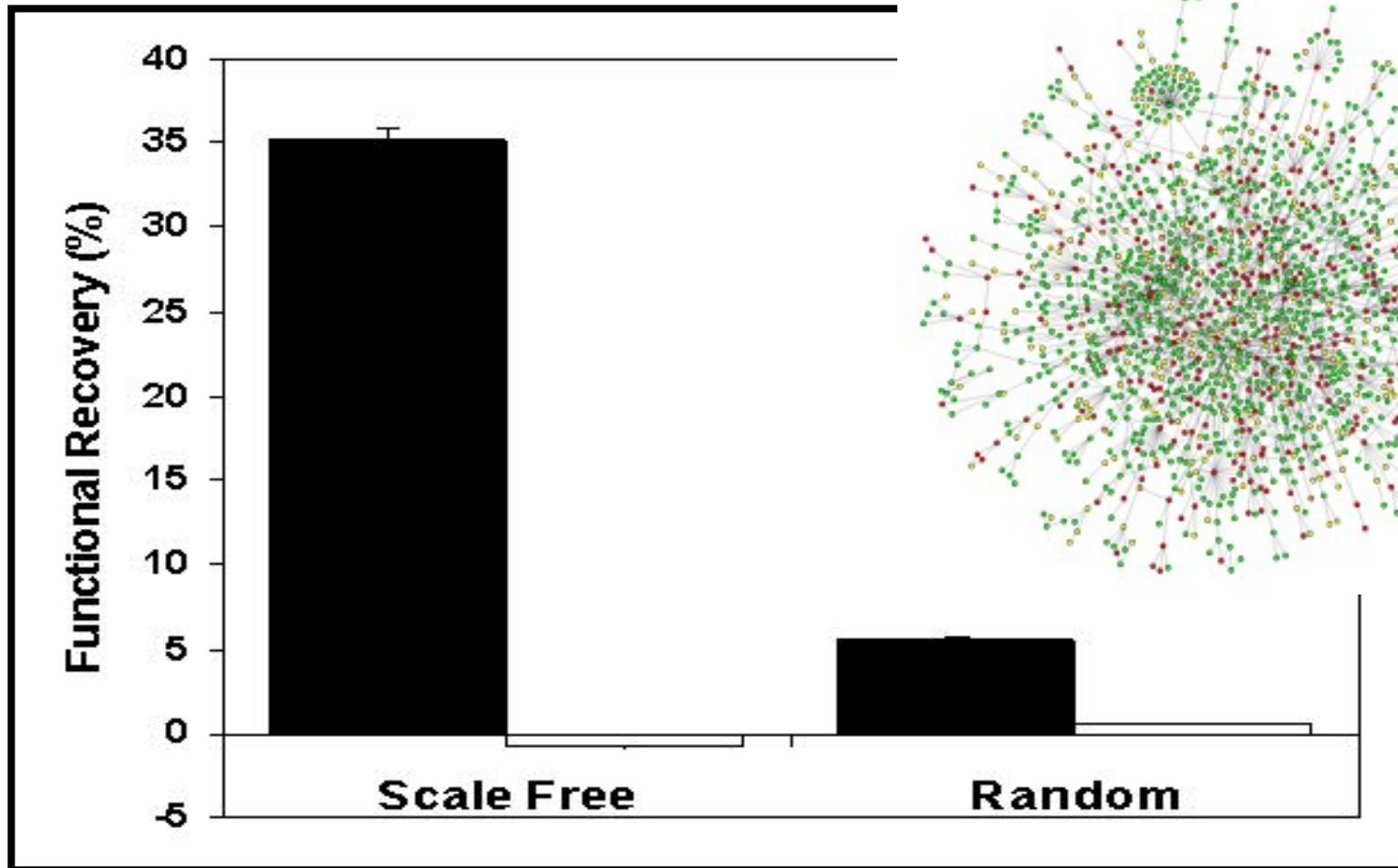
for

Pharmacological Interventions
on Cardiac Aging

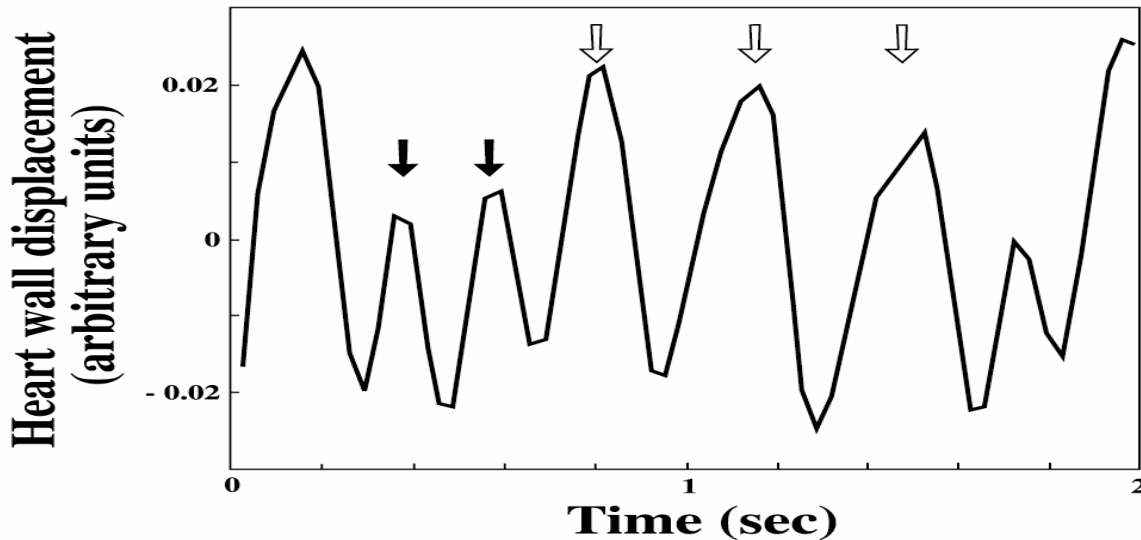
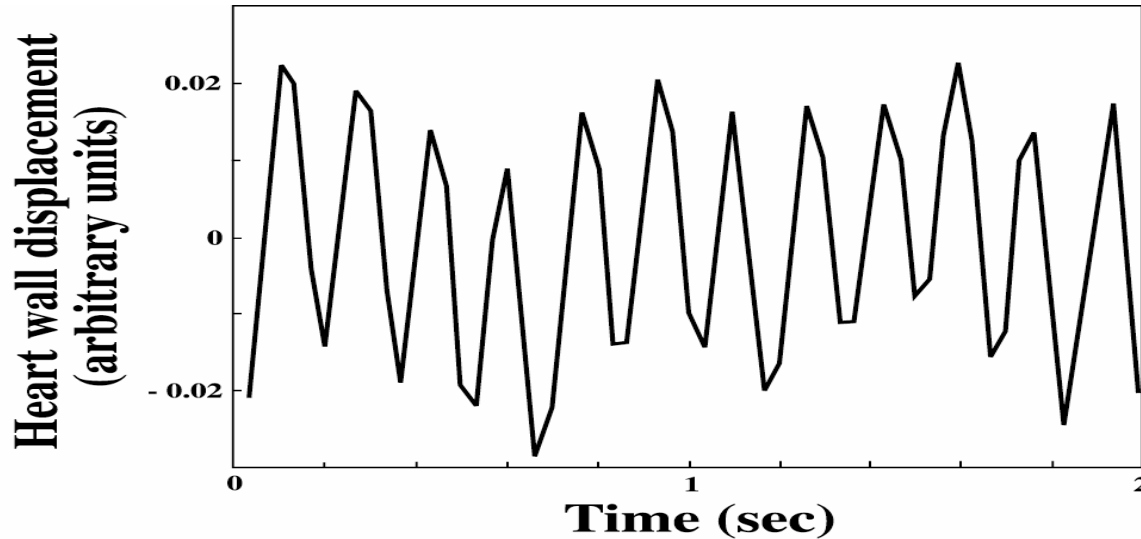
Andrew Viterbi

Jen Schofield

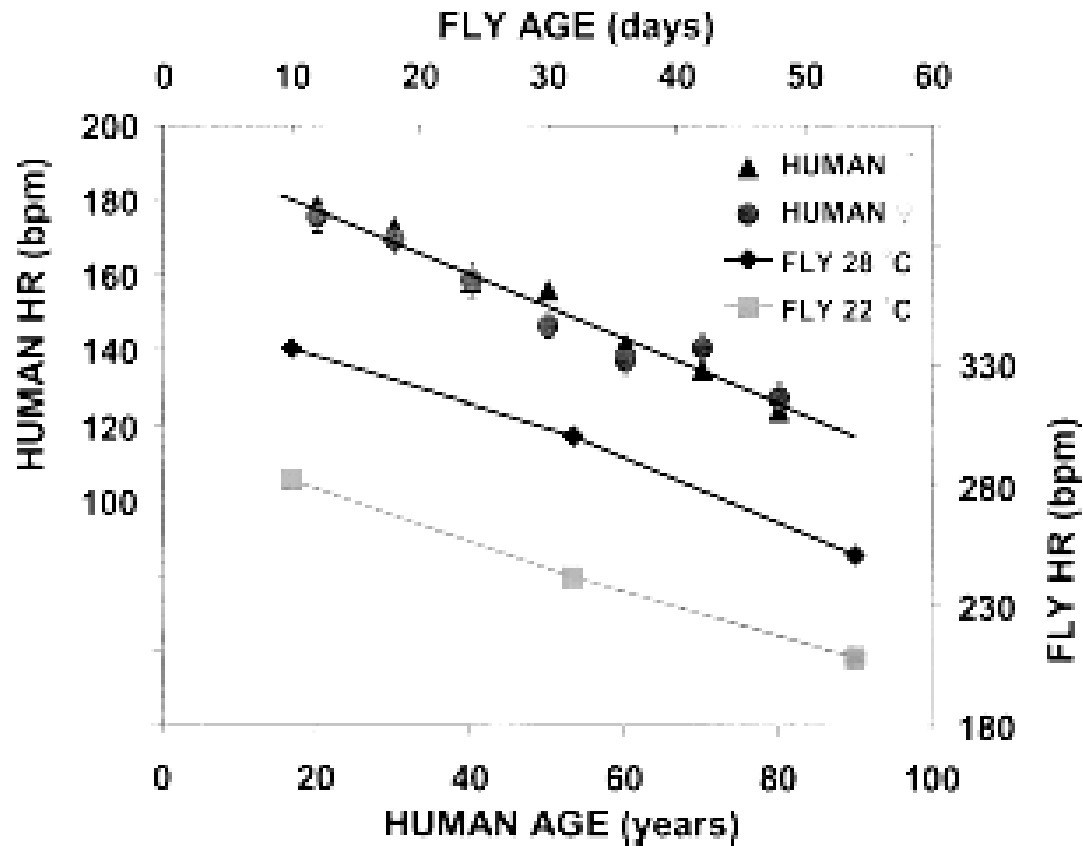
Interventions on hubs are sufficient to restore function



Automated detection of fly heart wall displacement

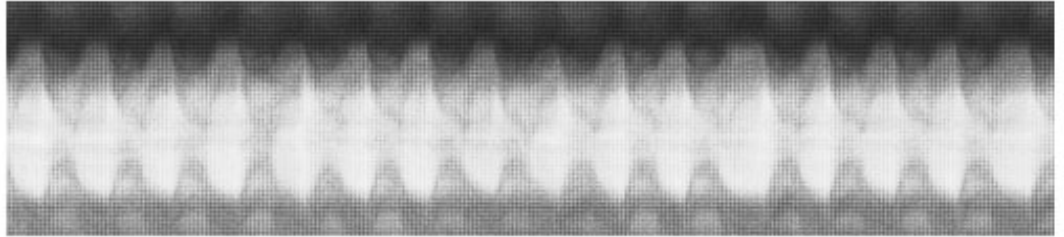


Human and fly cardiac changes with age



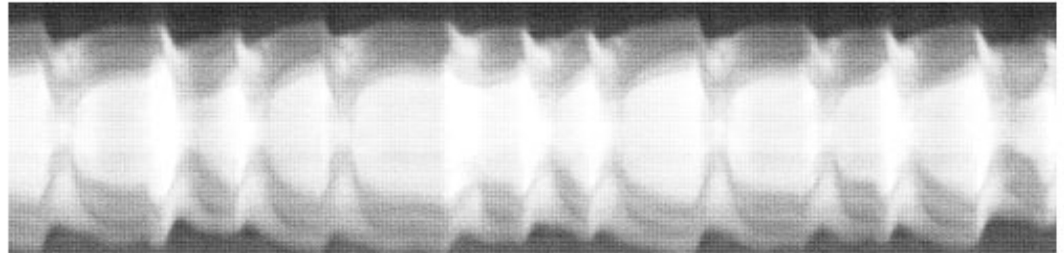
2-day-old fly

A)



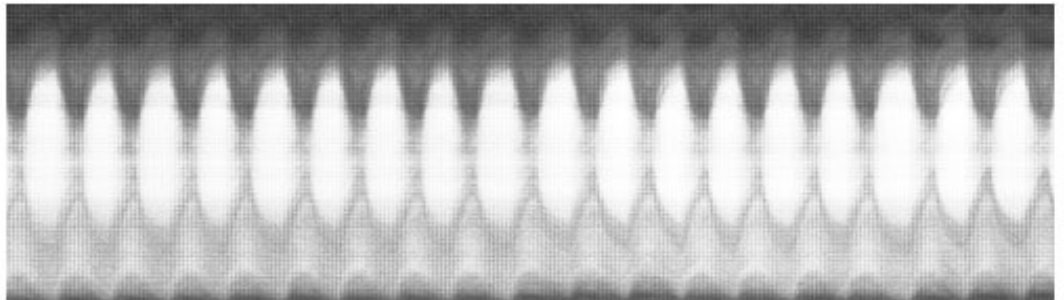
30-day-old fly

B)



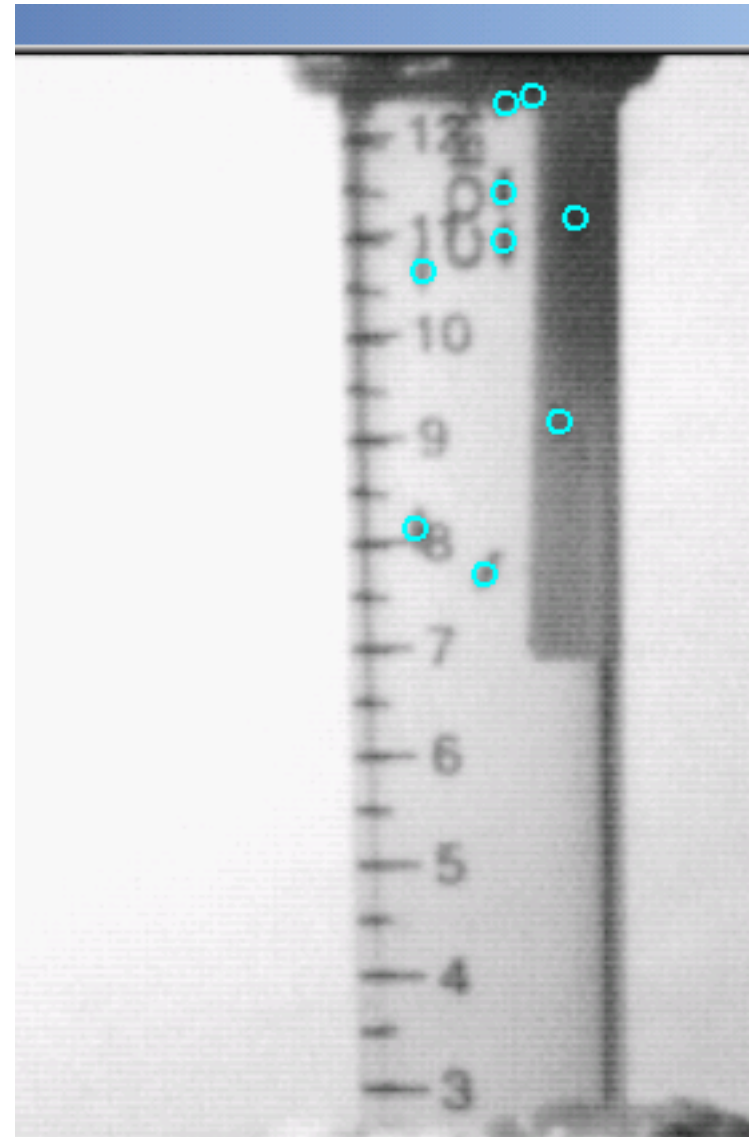
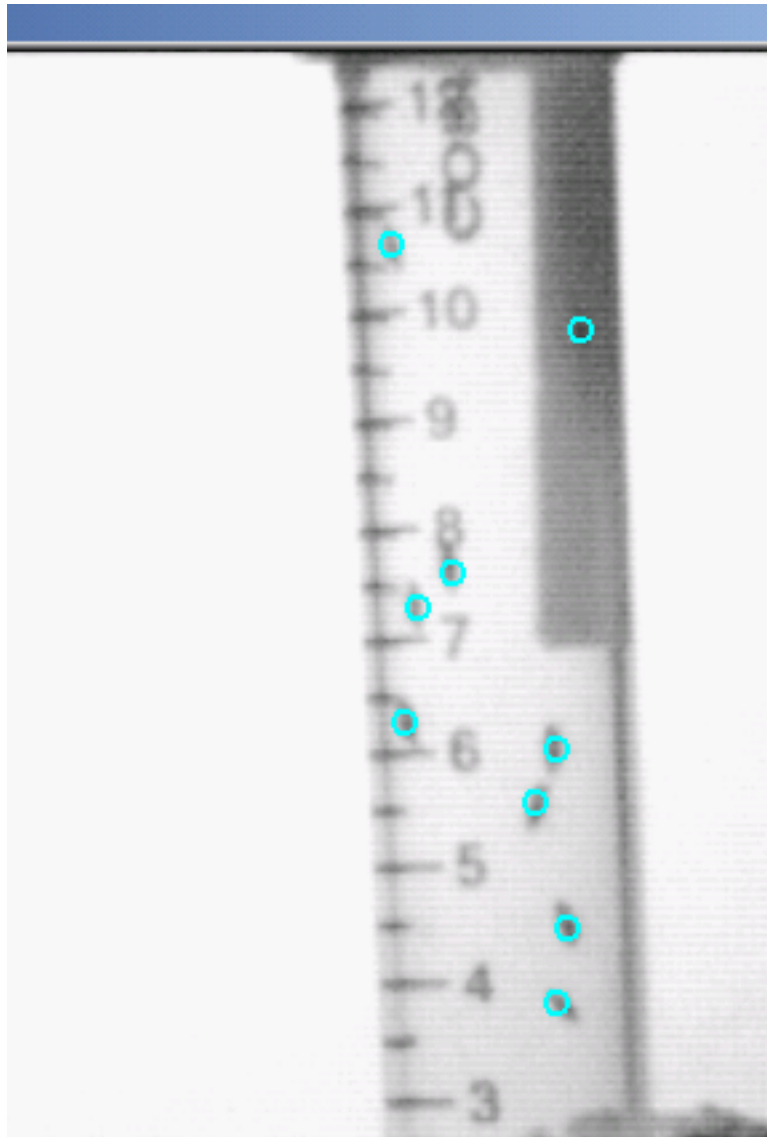
30-day-old fly
+ doxycycline

C)



Climbing Velocity at 30 days of age

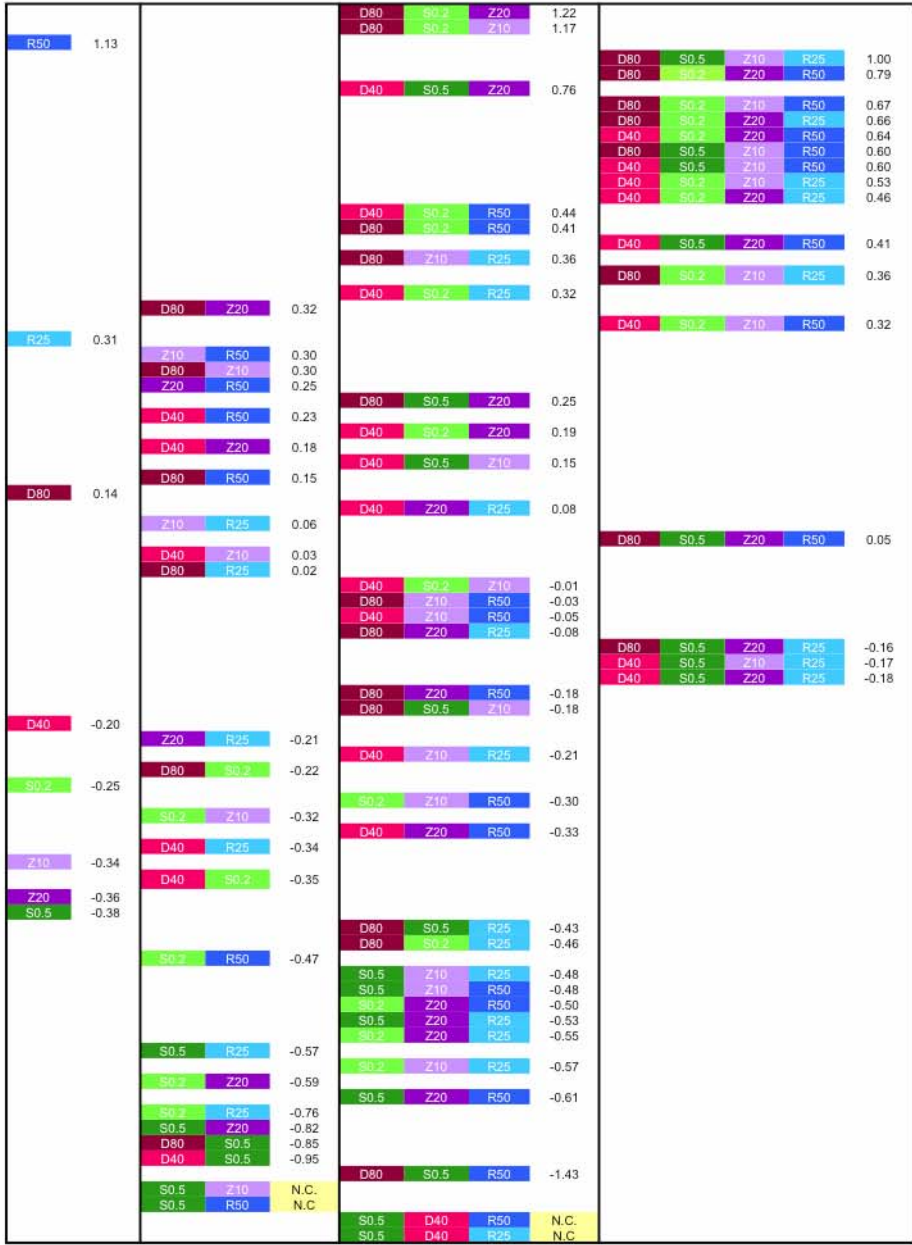
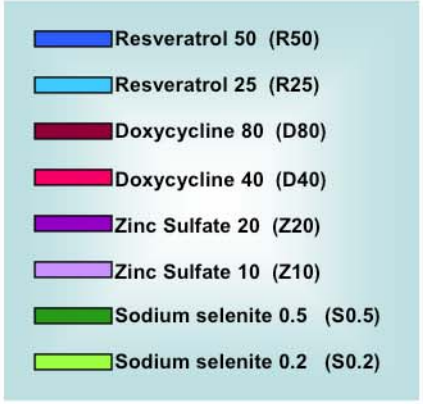
Resveratrol



Combinations (Fully factorial)

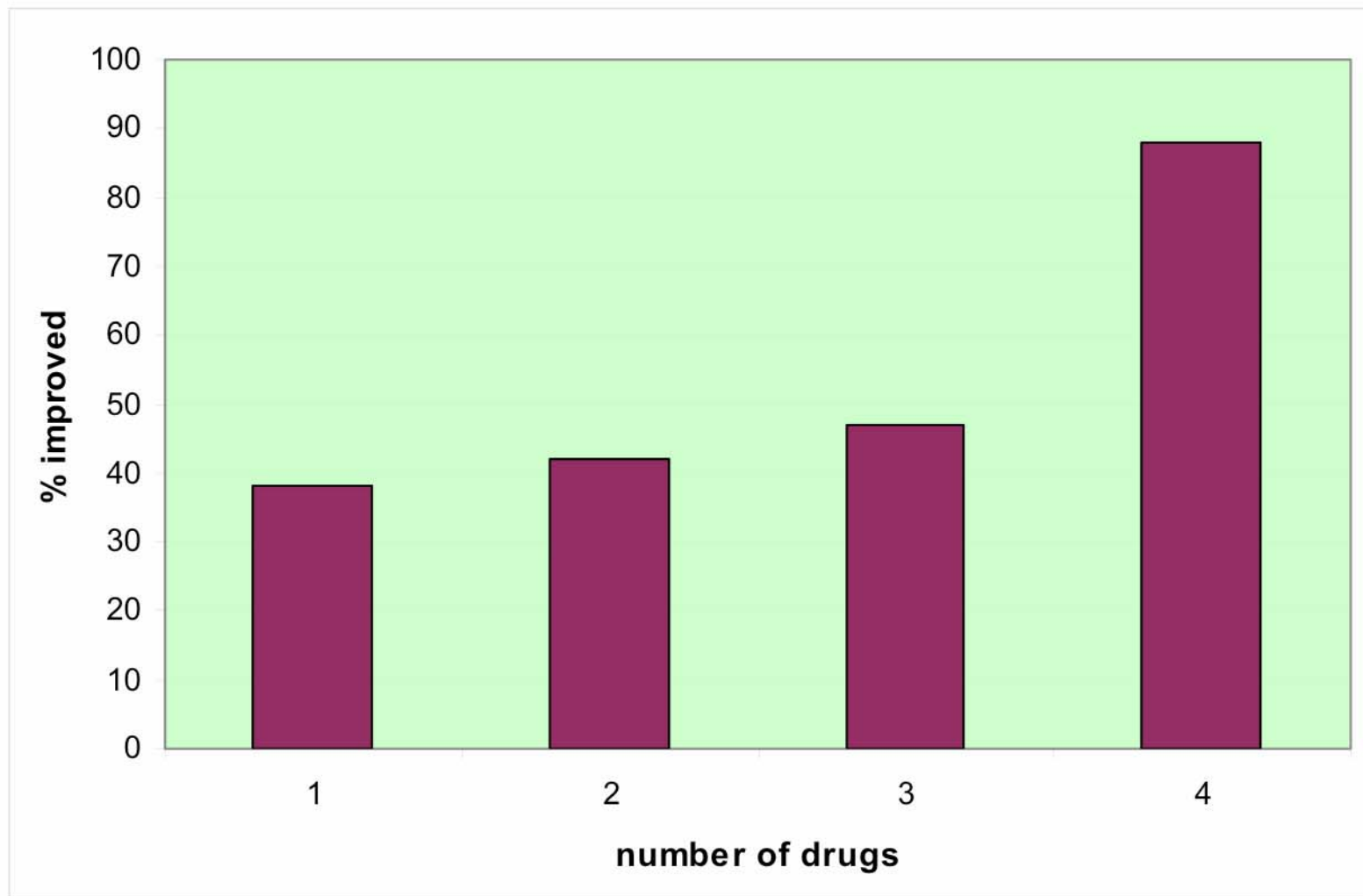
Number of drugs

	0	1	2	3	4	5	6	7	8	9	Total number of combinations
0	1										$3^0 = 1$
1	1	2									$3^1 = 3$
2	1	4	4								$3^2 = 9$
3	1	6	12	8							$3^3 = 27$
4	1	8	24	32	16						$3^4 = 81$
5	1	10	40	80	80	32					$3^5 = 243$
6	1	12	60	160	240	192	64				$3^6 = 729$
7	1	14	84	280	560	672	448	128			$3^7 = 2187$
8	1	16	112	448	1120	1792	1792	1024	256		$3^8 = 6561$
9	1	18	144	672	2016	4032	5376	4608	2304	512	$3^9 = 19683$



← CONTROL

N.C. = not classified



Stack Sequential

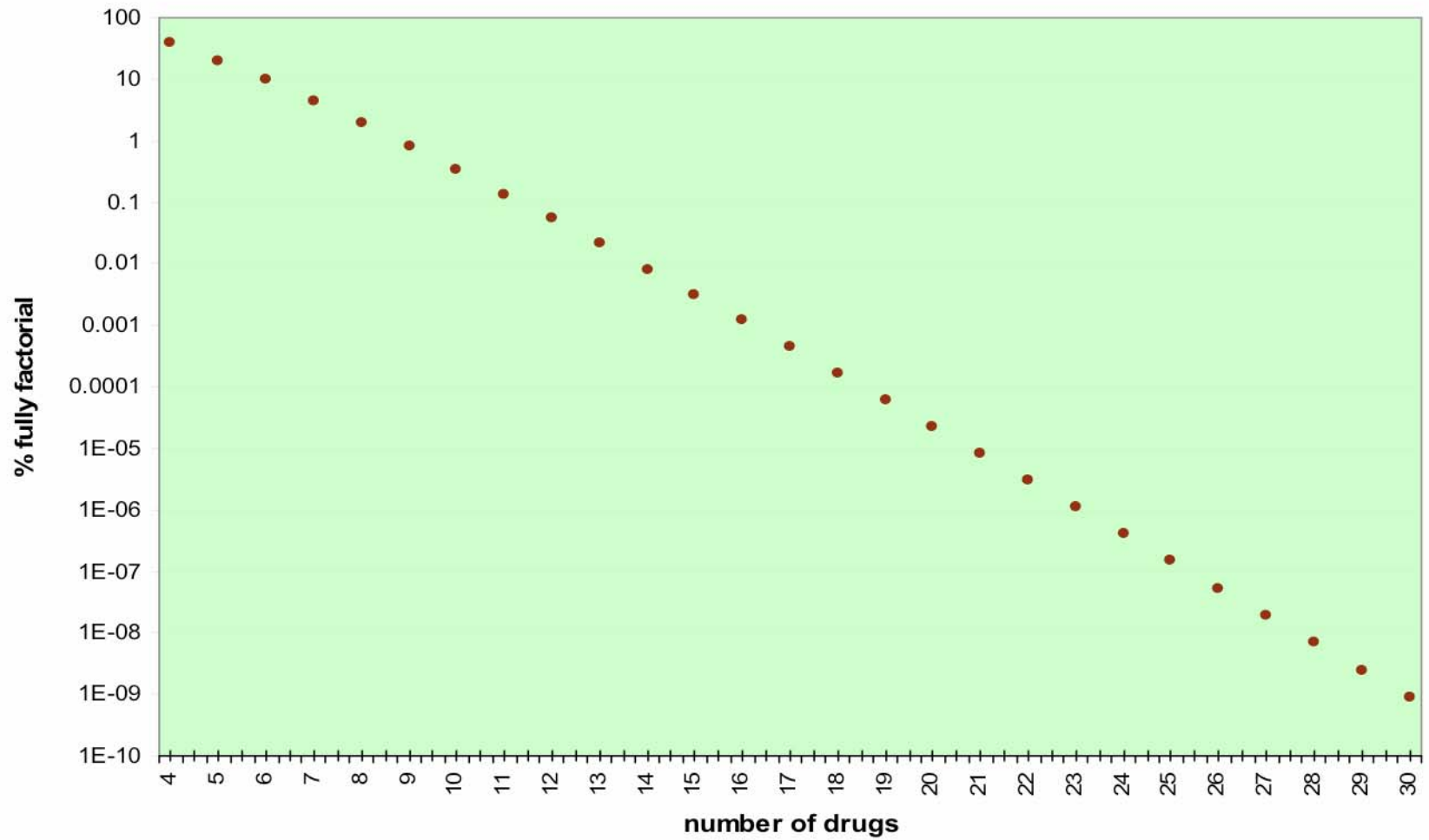
R50

D80-S0.2-Z20

D80-S0.2-Z20-R50

R50	1.13			D80-S0.2-Z20	1.22		
				D80-S0.2-Z10	1.17		
				D40-S0.5-Z20	0.76		D80-S0.5-Z10-R25
							D80-S0.2-Z20-R50
							D80-S0.2-Z10-R50
							D80-S0.2-Z20-R25
							D40-S0.2-Z20-R50
							D80-S0.5-Z10-R50
							D40-S0.5-Z10-R50
							D40-S0.2-Z10-R25
							D40-S0.2-Z20-R25
				D40-S0.2-R50	0.44		
				D80-S0.2-R50	0.41		D40-S0.5-Z20-R50
				D80-Z10-R25	0.36		D80-S0.2-Z10-R25
				D40-S0.2-R25	0.32		D40-S0.2-Z10-R50
				D80-Z20	0.32		
R25	0.31	Z10-R50	0.30	D80-S0.5-Z20	0.25		
		D80-Z10	0.30	D40-S0.2-Z20	0.19		
		Z20-R50	0.25	D40-S0.5-Z10	0.15		
		D40-R50	0.23	D40-Z20-R25	0.08		D80-S0.5-Z20-R50
		D40-Z20	0.18	D40-S0.2-Z10	-0.01		
		D80-R50	0.15	D80-Z10-R50	-0.03		
		Z10-R25	0.06	D40-Z10-R50	-0.05		
		D40-Z10	0.03	D80-Z20-R25	-0.08		D80-S0.5-Z20-R25
		D80-R25	0.02	D80-Z20-R50	-0.18		D40-S0.5-Z10-R25
				D80-S0.5-Z10	-0.18		D40-S0.5-Z20-R25
D40	-0.20	Z20-R25	-0.21	D40-Z10-R25	-0.21		
S0.2	-0.25	D80-S0.2	-0.22	S0.2-Z10-R50	-0.3		
		S0.2-Z10	-0.32	D40-Z20-R50	-0.33		
Z10	-0.34	D40-R25	-0.34				
Z20	-0.36	D40-S0.2	-0.35	D80-S0.5-R25	-0.43		
S0.5	-0.38			D80-S0.2-R25	-0.46		
		S0.2-R50	-0.47	S0.5-Z10-R25	-0.48		
				S0.5-Z10-R50	-0.48		
		S0.5-R25	-0.57	S0.2-Z20-R50	-0.50		
		S0.2-Z20	-0.59	S0.5-Z20-R25	-0.53		
		S0.2-R25	-0.76	S0.2-Z20-R25	-0.55		
		S0.5-Z20	-0.82	S0.2-Z10-R25	-0.57		
		D80-S0.5	-0.85	S0.5-Z20-R50	-0.61		
		D40-S0.5	-0.95				
		S0.5-Z10	N.C	D80-S0.5-R50	-1.43		
		S0.5-R50	N.C				
				S0.5-D40-R50	N.C		
				S0.5-D40-R50	N.C		

Stack sequential



Top Down

			D80-S0.2-Z20	1.22			
			D80-S0.2-Z10	1.17			
R50	1.13					D80-S0.5-Z10-R25	1.00
						D80-S0.2-Z20-R50	0.79
			D40-S0.5-Z20	0.76			
						D80-S0.2-Z10-R50	0.67
						D80-S0.2-Z20-R25	0.66
						D40-S0.2-Z20-R50	0.64
						D80-S0.5-Z10-R50	0.60
						D40-S0.5-Z10-R50	0.60
						D40-S0.2-Z10-R25	0.53
						D40-S0.2-Z20-R25	0.46
			D40-S0.2-R50	0.44			
			D80-S0.2-R50	0.41		D40-S0.5-Z20-R50	0.41
			D80-Z10-R25	0.36			
			D40-S0.2-R25	0.32		D80-S0.2-Z10-R25	0.36
		D80-Z20	0.32				
						D40-S0.2-Z10-R50	0.32
R25	0.31	Z10-R50	0.30				
		D80-Z10	0.30				
		Z20-R50	0.25				
		D40-R50	0.23	D80-S0.5-Z20	0.25		
		D40-Z20	0.18	D40-S0.2-Z20	0.19		
		D80-R50	0.15	D40-S0.5-Z10	0.15		
D80	0.14						
		Z10-R25	0.06	D40-Z20-R25	0.08		
		D40-Z10	0.03			D80-S0.5-Z20-R50	0.05
		D80-R25	0.02				
				D40-S0.2-Z10	-0.01		
				D80-Z10-R50	-0.03		
				D40-Z10-R50	-0.05		
				D80-Z20-R25	-0.08		
						D80-S0.5-Z20-R25	-0.16
						D40-S0.5-Z10-R25	-0.17
						D40-S0.5-Z20-R25	-0.18
D40	-0.20			D80-Z20-R50	-0.18		
				D80-S0.5-Z10	-0.18		
		Z20-R25	-0.21	D40-Z10-R25	-0.21		
S0.2	-0.25	D80-S0.2	-0.22				
				S0.2-Z10-R50	-0.3		
		S0.2&Z10	-0.32	D40-Z20-R50	-0.33		
		D40-R25	-0.34				
Z10	-0.34	D40-S0.2	-0.35				
Z20	-0.36						
S0.5	-0.38						
				D80-S0.5-R25	-0.43		
				D80-S0.2-R25	-0.46		
				S0.5-Z10-R25	-0.48		
				S0.5-Z10-R50	-0.48		
				S0.2-Z20-R50	-0.50		
				S0.5-Z20-R25	-0.53		
				S0.2-Z20-R25	-0.55		
		S0.5-R25	-0.57	S0.2-Z10-R25	-0.57		
		S0.2-Z20	-0.59	S0.5-Z20-R50	-0.61		
		S0.2-R25	-0.76				
		S0.5-Z20	-0.82				
		D80-S0.5	-0.85				
		D40-S0.5	-0.95				
				D80-S0.5-R50	-1.43		
		S0.5-Z10	N.C				
		S0.5-R50	N.C				
				S0.5-D40-R50	N.C		
				S0.5-D40-R50	N.C		

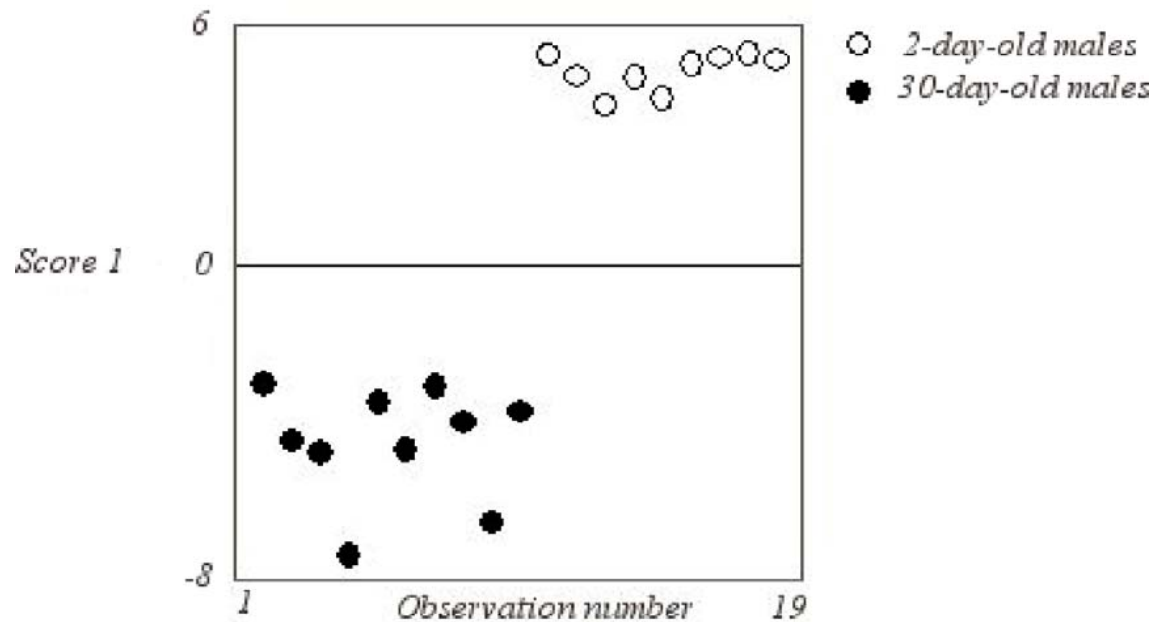
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8	1	16	112	448	1120	1792	1792	1024	256		$3^8 = 6561$
9	1	18	144	672	2016	4032	5376	4608	2304	512	$3^9 = 19683$

Multivariate Analysis

Reduction of Dimensionality



Molecular Algorithms for combining therapeutic interventions on aging

Multi-objective optimization - list of interventions

Fully factorial datasets

Robustness (reproducibility) between species

Integrating -omics data

Information theory - spread network pharmacology

www.paternostrolab.org