Some Idiosyncratic Responses to HINet Priority Questions

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Definitions of outcomes/phenotypes:

What is ‘Health’?
What are its Biological Correlates?

What is Health?

WHO Charter, 1948"

"A state of complete physical, mental, and social **well-being** and not just the absence of disease or infirmity"

Oxford English Dictionary (Online)

1a - "soundness of body; that condition in which its functions are efficiently discharged.- 1000 AD

4 - spiritual, moral , or mental soundness, **well-being. –** 1000 AD

5 - **well-being**, welfare, safety; deliverance".

-- 1250 AD

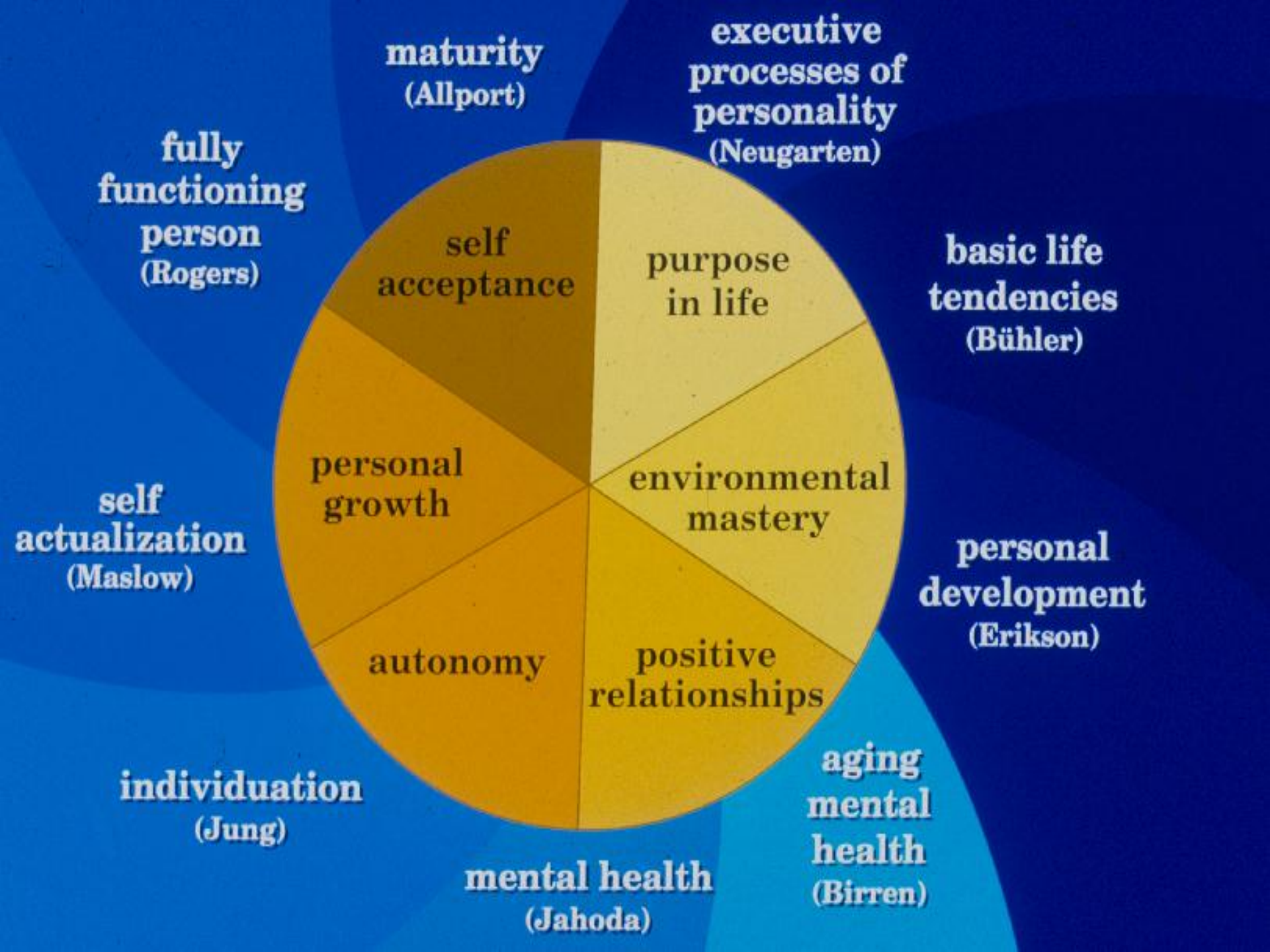
What is Well-Being?

- purposeful engagement
- positive self-regard
- good quality relationships
- environmental mastery
- continued growth

Eudaimonic

- happiness
- life satisfaction

Hedonic


maturity
(Allport)
executive processes of personality
(Neugarten)
fully functioning person
(Rogers)
basic life tendencies
(Bühler)
self acceptance
purpose in life
personal growth
environmental mastery
self actualization
(Maslow)
personal development
(Erikson)
autonomy
positive relationships
individuation
(Jung)
aging mental health
(Birren)
mental health
(Jahoda)

Canadian Mental Health – Statistics Canada

	Population estimate (thousands)	Positive mental health			
		High sense of coherence (%)	High self-esteem (%)	High mastery (%)	Happy, interested in life (%)
TOTAL	23,949	31	52	23	74
Males	11,780	32	53	25	74
Females	12,168	30	51	21	74
Ages 12–19	3,372	12	44	18	72
Ages 20–29	3,879	21	51	25	72
Ages 30–39	5,210	27	54	24	76
Ages 40–49	4,235	30	56	26	72
Ages 50–59	2,825	35	57	21	77
Ages 60–69	2,282	43	51	19	76
Ages 70+	2,145	47	48	18	73
Less than high scho	7,986	33	45	16	70
High school	9,007	28	53	23	74
College	3,806	30	55	25	76
University	3,109	34	63	34	81
Newfoundland	483	39	37	14	76
Prince Edward Islan	110	35	42	19	82
Nova Scotia	764	30	39	21	73
New Brunswick	626	29	44	15	75
Quebec	6,030	27	66	24	72
Ontario	9,050	32	51	24	74
Manitoba	891	34	36	14	74
Saskatchewan	792	37	36	17	75
Alberta	2,166	30	47	24	78
British Columbia	3,037	30	49	23	73

Canadian Mental Health – Statistics Canada

	Population estimate (thousands)	Mental health problems			
		Depressed (%)	High distress level (%)	Distress affects life (%)	Some cognitive impairment (%)
TOTAL	23,949	6	29	16	9
Males	11,780	4	26	14	9
Females	12,168	7	32	18	9
Ages 12–19	3,372	7	40	17	13
Ages 20–29	3,879	7	38	17	9
Ages 30–39	5,210	6	29	15	7
Ages 40–49	4,235	6	25	16	9
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Prince Edward Islan	110	#	23	#	6
Nova Scotia	764	8	27	19	11
New Brunswick	626	4	28	17	11
Quebec	6,030	5	35	13	6
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Regular Article

Psychotherapy and Psychosomatics

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Psychological Well-Being and Ill-Being: Do They Have Distinct or Mirrored Biological Correlates?

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Table 3. Ill-being, well-being and biomarkers: distinct or mirrored associational patterns

Correlation of *ill-being* with biomarkers	Correlation of **well-being** with biomarkers: Positive associations	No associations	Negative associations
Positive associations	*Anger* ⇦ **Epinephrine** ⇨ Positive relations	*Depressive symptoms** ⇦ **DHEA-S**	*Negative affect* ⬅ **Glycosylated hemoglobin** ➡ Positive relations *Anxiety* *Anger* *Depressive symptoms* ⬅ **Weight** ➡ Positive relations
No associations	**Cortisol** ⇨ Purpose in life, Personal growth **Norepinephrine** ⇨ Autonomy **HDL cholesterol** ⇨ Purpose in life, Personal growth, Positive affect		**Waste-hip ratio** ➡ Positive relations, ⇨ Purpose in life **Total HDL cholesterol** ⇨ Personal growth
Negative associations		*Negative affect* *Anxiety** *Anger* ⇦ **Systolic blood pressure**	

▭ Distinct associational patterns; ▭ mirrored associational patterns.

⇨ Correlation is significantly different from zero (arrow pointing left = associations with *ill-being*, arrows pointing right = associations with well-being).

➡ Significant differences between correlation coefficients, adjusted for multiple comparisons by controlling the false discovery rate at 0.05.

* Age 75+ only.

Psychobiology and molecular genetics of resilience

Adriana Feder, Eric J. Nestler‡ and Dennis S. Charney‡*

Abstract | Every individual experiences stressful life events. In some cases acute or chronic stress leads to depression and other psychiatric disorders, but most people are resilient to such effects. Recent research has begun to identify the environmental, genetic, epigenetic and neural mechanisms that underlie resilience, and has shown that resilience is mediated by adaptive changes in several neural circuits involving numerous neurotransmitter and molecular pathways. These changes shape the functioning of the neural circuits that regulate reward, fear, emotion reactivity and social behaviour, which together are thought to mediate successful coping with stress.

Source: *Nature Reviews Neuroscience* (June, 2009)

How should we deal with multiple exposures?

An associated question:

How should we operationalize "Allostatic Load"?

***Allostasis*$_1$ – Variation in system parameters to maintain homeostasis**

***Allostasis*$_2$ – Variation in system parameters to maintain stability**

***Allostatic State* – A state of chronic deviation of the regulatory system from its normal operating level, measured via primary mediators**

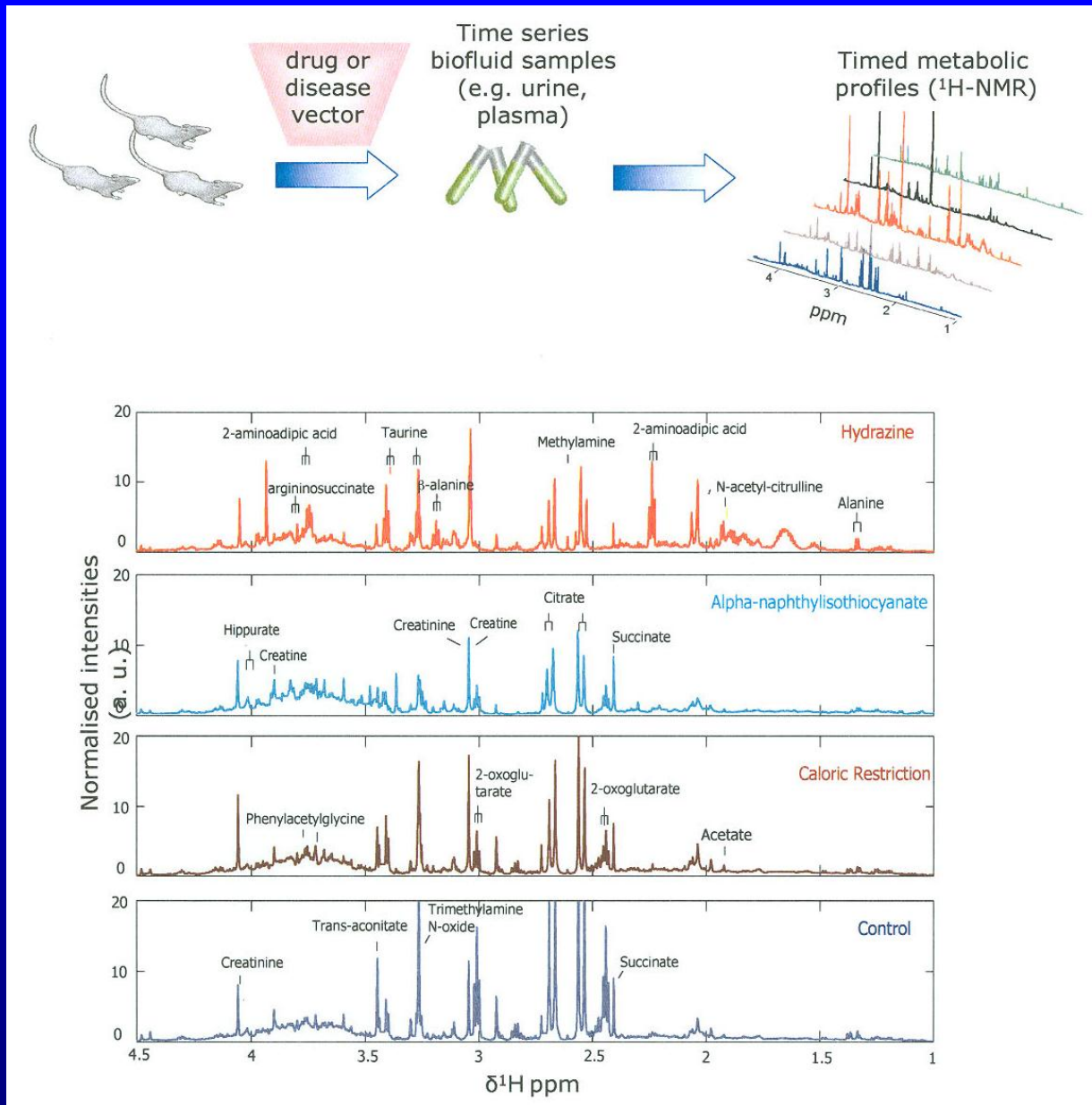
Primary Mediators -- ***(i) elevated levels of inflammatory cytokines; (ii) elevated and flattened diurnal cortisol rhythms, and elevated overnight urinary cortisol; (iii) elevated levels of overnight urinary catecholamines; (iv) abnormal insulin levels (also assessed indirectly as abnormal glucose levels), ….., etc.***

***Allostatic Load*$_1$ – The cost to the brain and the body of the deviation from normal conditions, accumulating over time, and reflecting in many cases pathological states and accumulation of damage**

***Allostatic Load*$_2$ – Cumulative changes that reflect continued operation of the allostatic state or overactivation of allostatic responses [Measures of allostatic load are secondary outcomes]**

***Secondary Outcomes* – Brain: atrophy of brain regions, cognitive impairment**
Cardiovascular: atherosclerosis, left ventricular hypertrophy, oxidative stress markers
Immune System: impaired wound healing, retarded immunization response
Metabolic: elevated HbA1c, low HDL:LDL ratio, high waist-hip ratio

Trajectories of Metabolic Risk via NMR Spectroscopy


drug or disease vector
Time series biofluid samples (e.g. urine, plasma)
Timed metabolic profiles (¹H-NMR)
ppm
Hydrazine
2-aminoadipic acid
Taurine
Methylamine
2-aminoadipic acid
argininosuccinate
β-alanine
, N-acetyl-citrulline
Alanine
Alpha-naphthylisothiocyanate
Hippurate
Creatine
Creatinine
Creatine
Citrate
Succinate
Caloric Restriction
Phenylacetylglycine
2-oxoglu-tarate
2-oxoglutarate
Acetate
Control
Trans-aconitate
Trimethylamine N-oxide
Creatinine
Succinate
Normalised intensities (a. u.)
δ¹H ppm

The idea of Recovery Potential

Let C_i = concentration of metabolite i during challenge

Let C_{i0} = concentration of metabolite i at baseline

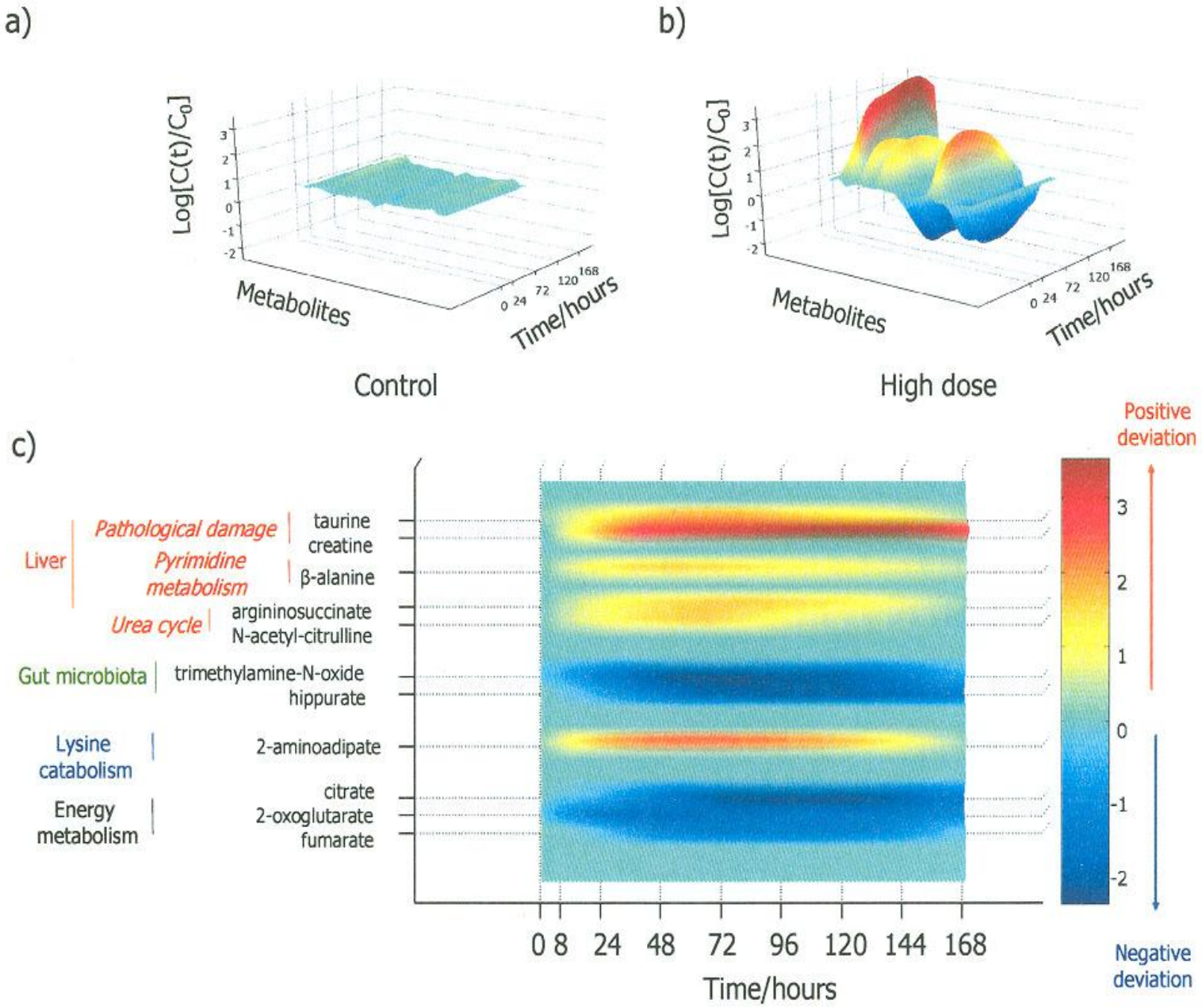
$$w_i = 1/Var(C_{i0})$$

Define Recovery Potential as:

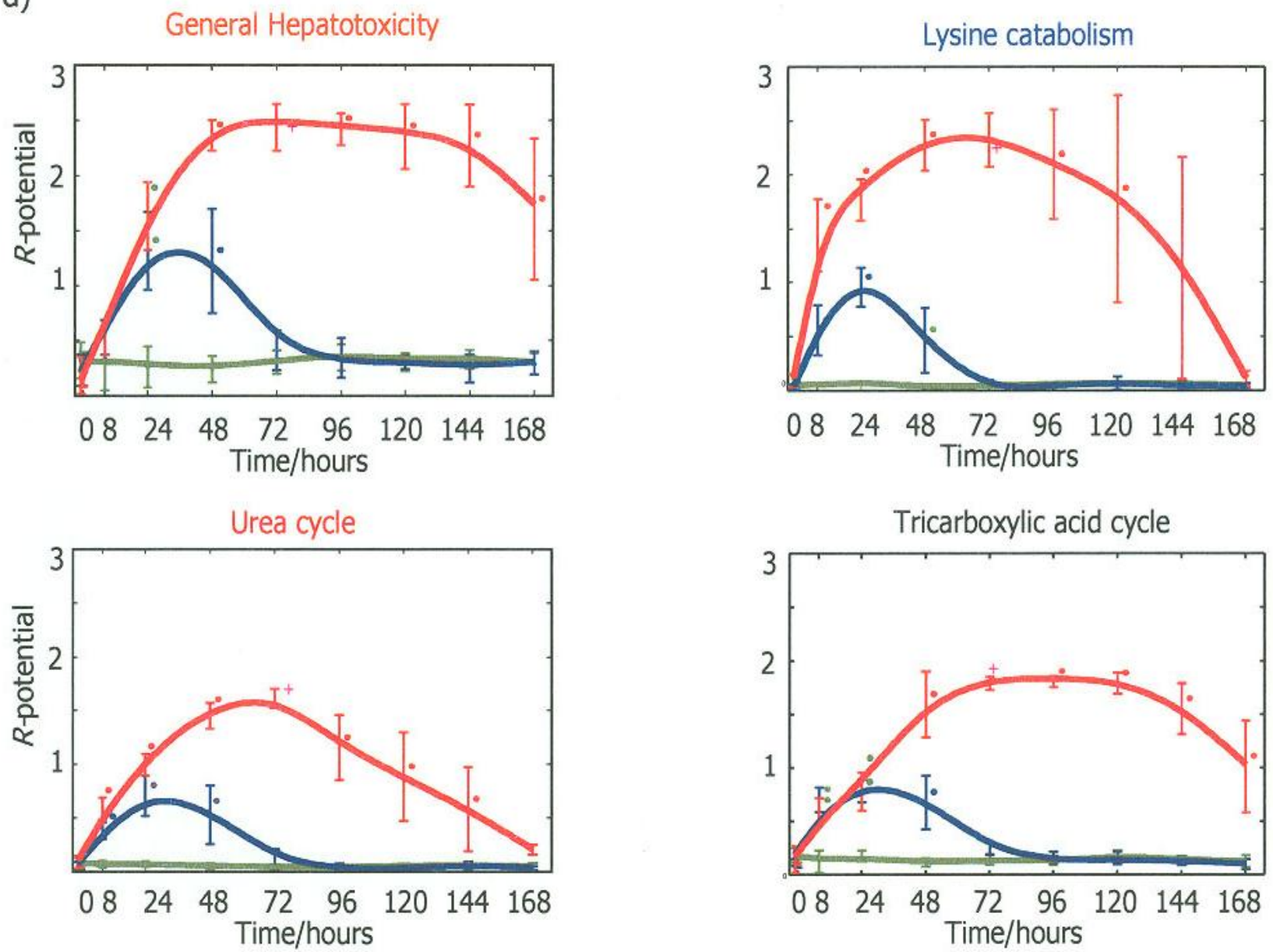
$$R = \sum w_i \left| \log [C_i/C_{i0}] \right|$$

{Summation is over metabolites known to be involved in a given challenge}

Interpretation: The counteracting response that must be exerted by allostatic mechanisms (i.e. the process of allostasis) to recover from perturbed metabolic functions – work required to restore metabolic systems to baseline conditions


a)
b)
Log[C(t)/C0]
Metabolites
Time/hours
0 24 72 120 168
Control
High dose
c)
Positive deviation
Negative deviation
Liver
Pathological damage
Pyrimidine metabolism
Urea cycle
Gut microbiota
Lysine catabolism
Energy metabolism
taurine
creatine
β-alanine
argininosuccinate
N-acetyl-citrulline
trimethylamine-N-oxide
hippurate
2-aminoadipate
citrate
2-oxoglutarate
fumarate
0 8 24 48 72 96 120 144 168
Time/hours

d)


General Hepatotoxicity
Lysine catabolism
Urea cycle
Tricarboxylic acid cycle
R-potential
Time/hours
0 8 24 48 72 96 120 144 168
1
2
3

Metabolic Entropy

From a histogram based on values of

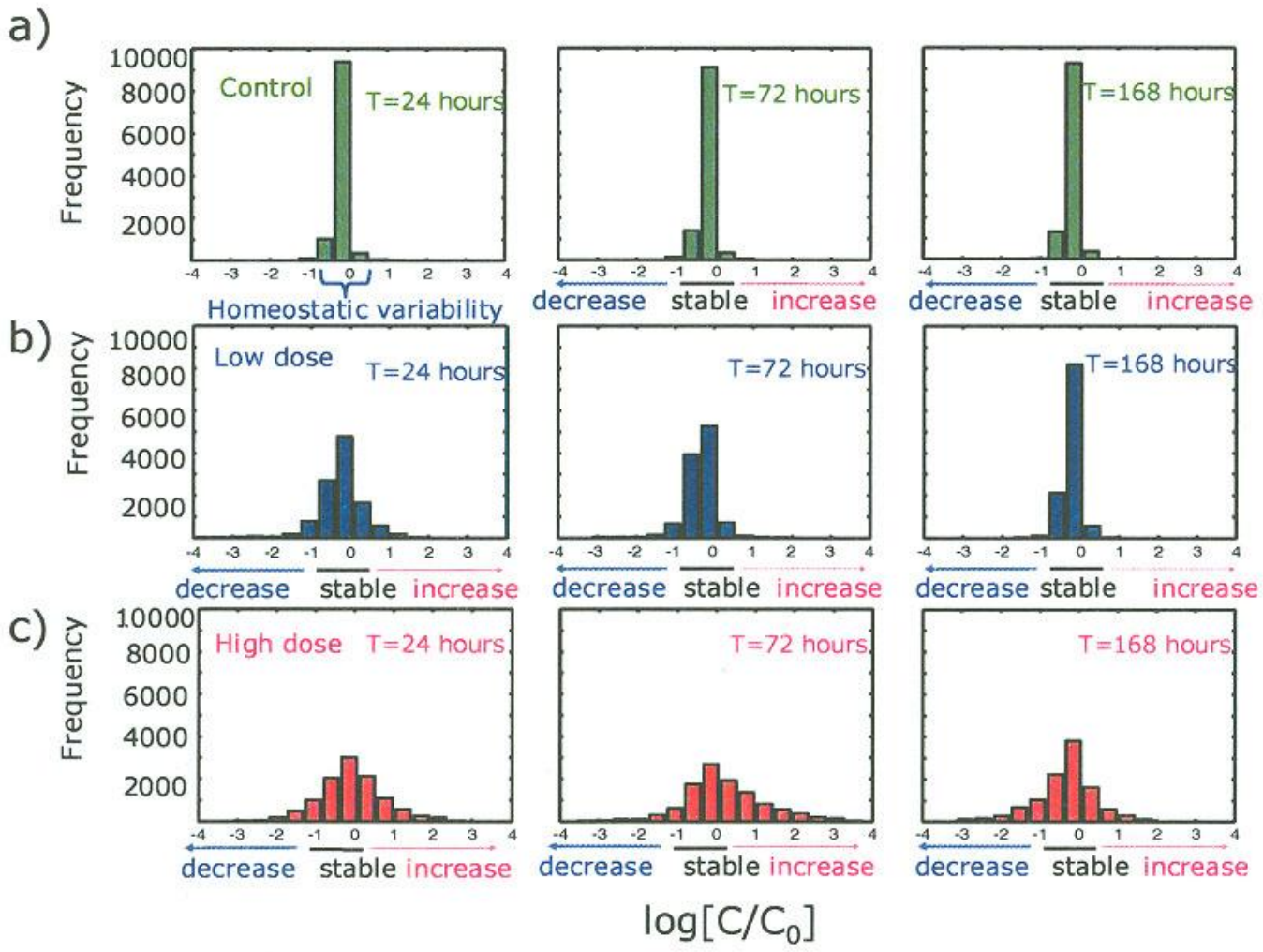
$x_i(t) = \log [C_i(t)/C_{i0}(t)]$, *define*

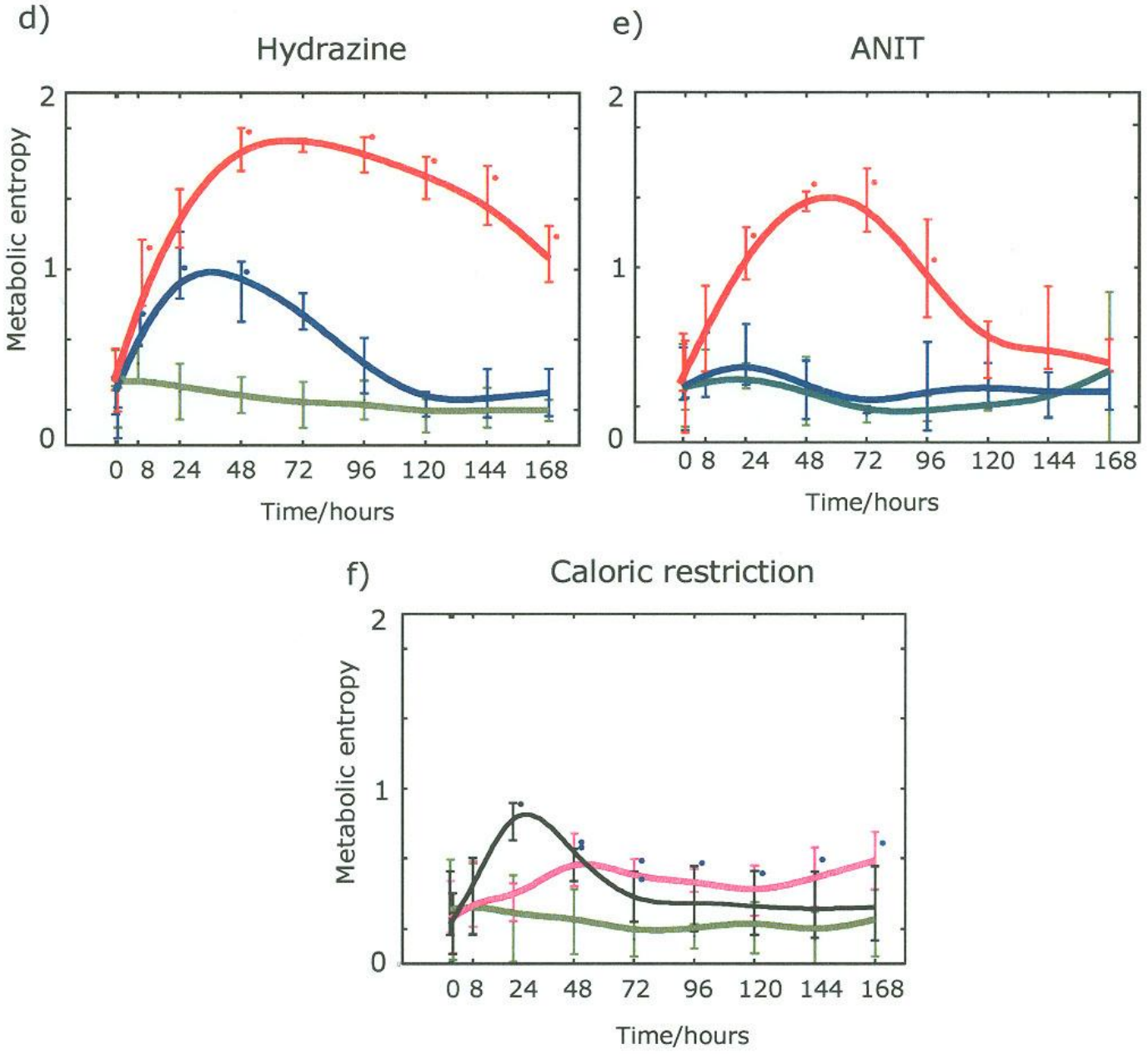
$p_j(t)$ = *proportion of metabolites with* $x_i(t)$ *in bin j of the histogram. Then define* ***METABOLIC ENTROPY*** *via*

$$S_m(t) = \sum p_j(t) \log p_j(t)$$

where the summation is over bins of the histogram.

Interpretation -- Metabolic Entropy is a measure of disorder among metabolic systems


a)
b)
c)
Frequency
10000
8000
6000
4000
2000
Control
T=24 hours
T=72 hours
T=168 hours
Homeostatic variability
Low dose
High dose
decrease
stable
increase
-4 -3 -2 -1 0 1 2 3 4
log[C/C0]


d)
Hydrazine
Metabolic entropy
2
1
0
0 8 24 48 72 96 120 144 168
Time/hours
e)
ANIT
2
1
0
0 8 24 48 72 96 120 144 168
Time/hours
f)
Caloric restriction
Metabolic entropy
2
1
0
0 8 24 48 72 96 120 144 168
Time/hours

Allostatic Load – Metabolic Version

Let S = metabolic entropy when the organism has all metabolites with concentrations in normal range. Then define* $\rho(t) = S_m(t)/S^*$. *If* $\rho(t)$ *is sufficiently large – i.e.* $\rho(t) >$ *some threshold, c – we say that allostatic load is accumulating. Formally, we set* $\rho^*(t) = \rho(t)$ *when* $\rho(t) > c$ *and* $= 0$ *otherwise.*

Then we define ***ALLOSTATIC LOAD*** *over the time interval from* T_1 *to* T_2 *as*

$$\int \rho^*(t)dt$$

where integration is over the interval $[T_1, T_2]$.

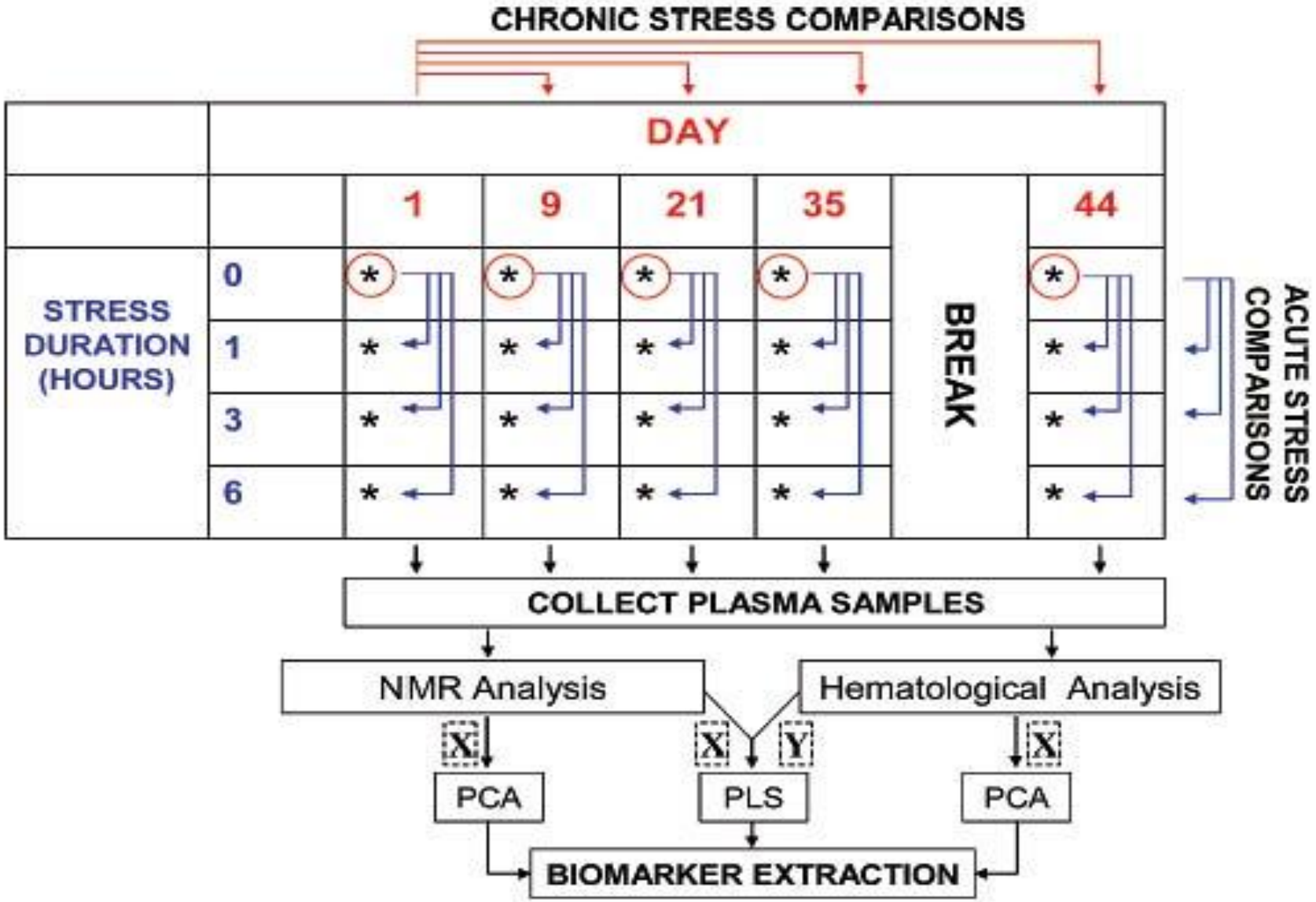


Figure 1. Schematic showing general experimental and analytical sampling strategy for PCA- and PLS-oriented modeling of the metabolic consequences of acute and chronic stress conditions.

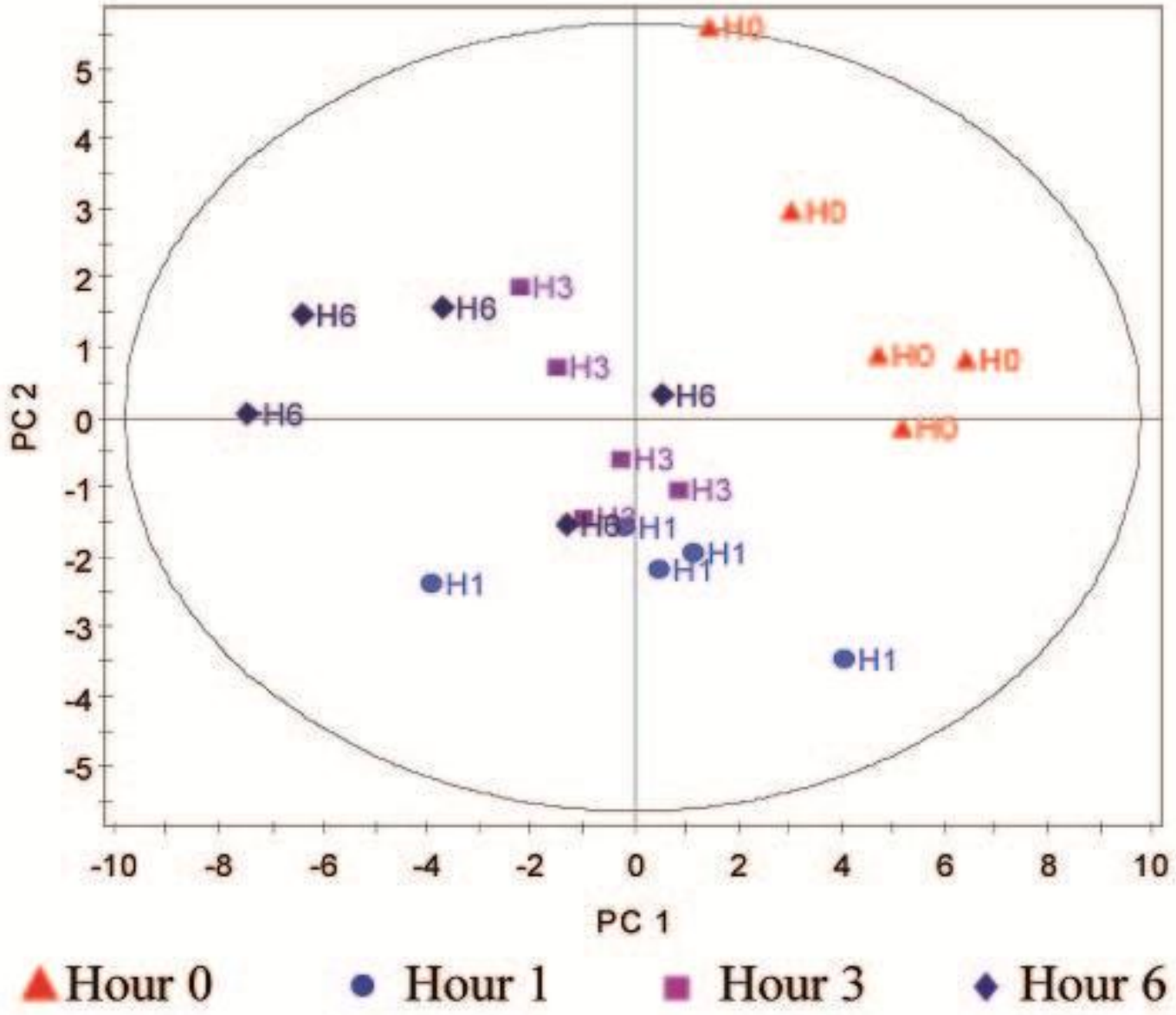


Figure 4. PCA scores map for data derived from the CPMG spin–echo ^{1}H NMR spectra of plasma obtained from acutely stressed animals on day 1 of the restraint stress, and separated based on the collection time-point.

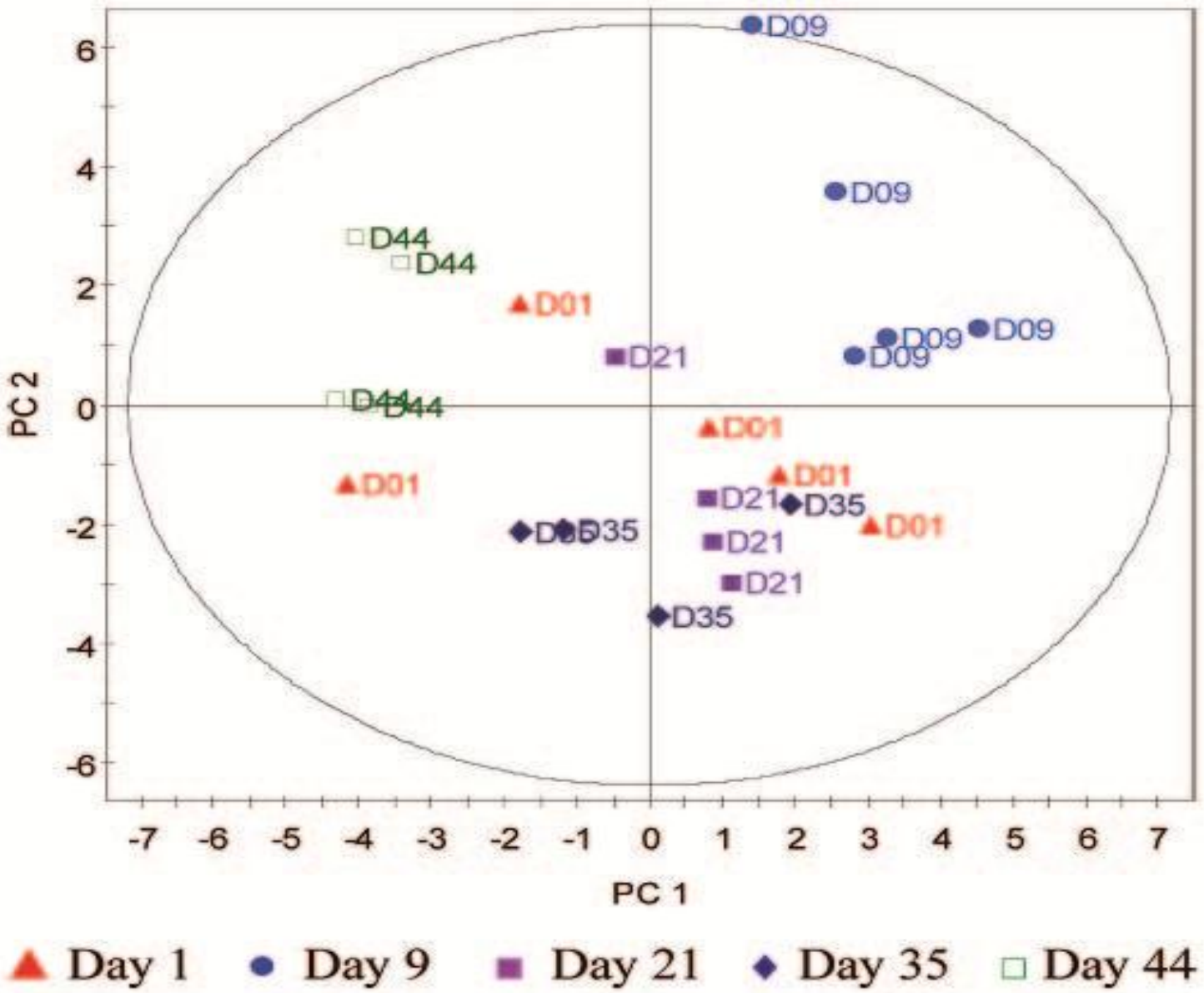


Figure 5. PCA scores map for data derived from the CPMG spin–echo ^{1}H NMR spectra of plasma obtained from chronically stressed animals at hour 0 of the study, and separated based on the length of the chronic stress.

groups	COR μg/100 mL
Control 0 h, day 1 ($n = 5$)	7.8 ± 1.9
Acute 1 h ($n = 5$)	$47.6 \pm 3.0^{***}$
Acute 3 h ($n = 5$)	$32.1 \pm 5.8^{***}$
Acute 6 h ($n = 5$)	$39.7 \pm 4.9^{***}$
Chronic day 9 ($n = 5$)	$20.0 \pm 4.8^{*}$
Chronic day 21 ($n = 4$)	$19.7 \pm 4.3^{*}$
Chronic day 35 ($n = 4$)	$14.0 \pm 0.8^{*}$
Chronic day 44 ($n = 4$)	8.9 ± 3.7

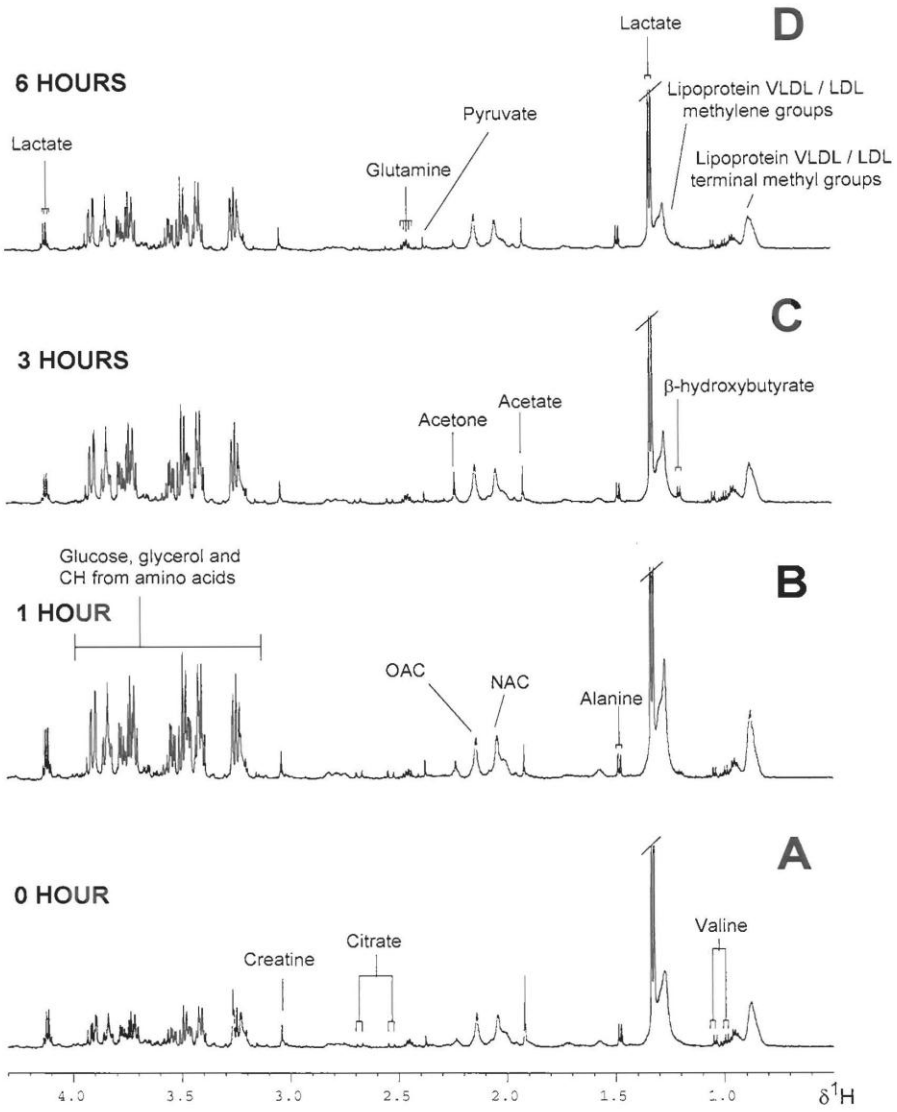


Figure 1: 600 MHz ^{1}H NMR CPMG spin-echo spectra (δ 4.3-0.5) of plasma samples collected from male Sprague Dawley rats at (A) pre-stress, (B) 1 hour, (C) 3 hours and (D) 6 hours following onset of restraint stress.

Abbreviations: OAC, O-acetylglycoproteins; NAC, N-acetylglycoproteins; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

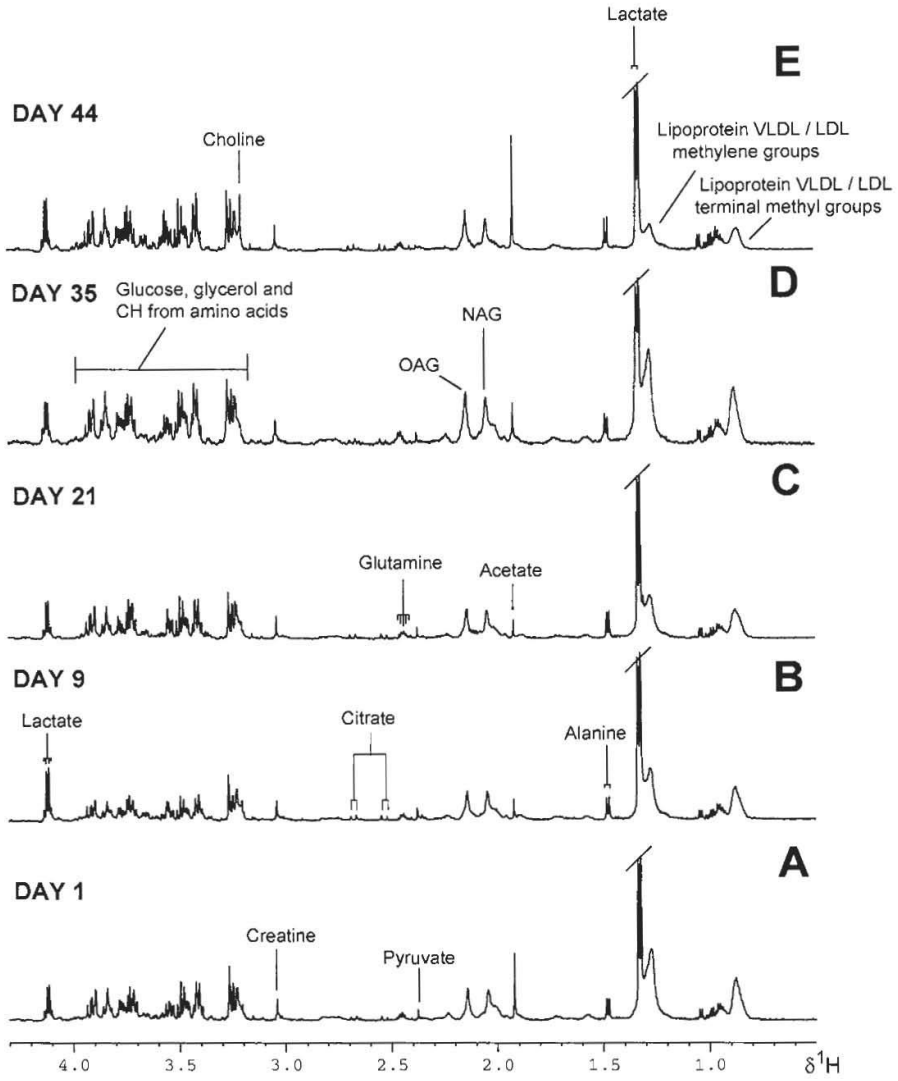


Figure 2: 600 MHz ^{1}H NMR CPMG spin-echo spectra (δ 4.3-0.5) of plasma samples collected from male Sprague Dawley rats at time = 0 hours, (A) pre-stress, (B) 9 days, (C) 21 days, (D) 35 days , and (E) 44 days after onset of the restraint stress.

Abbreviations: OAC, O-acetylglycoproteins; NAC, N-acetylglycoproteins; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.