Hybrid Population Simulations for Teaching Research Methodology

Michael Bulmer

School of Mathematics & Physics
University of Queensland

m.bulmer@uq.edu.au

Motivation

- Student experiments provide a context for learning statistical reasoning and introduce topics in study design
- They give an appreciation of the practical issues involved in carrying out experiments and collecting data
- However in student experiments raise logistical and ethical issues

The Islands

- The original *Island* launched in 2009
- An online environment where students can conduct studies involving virtual human subjects
- Provides a genetic history and background story for each Islander
- Students then propose treatments and measurements for enabling experimental studies

Islands Tour

Deliberate Omissions

The Islands don't *do* anything…

- No tools for choosing random samples
- No tools for applying tasks to multiple Islanders
- No display of combined data
- No statistical tools
- No content

Simulations

- The Islands are based on three simulations running at different timescales:
  - **Daily (shared)**
    Responsible for the overall history of the population
  - **Daily (individual)**
    Keeps track of a small number of medium-term experimental effects that students required
  - **Every 30 seconds (individual)**
    Models a range of physiological processes

Example Models

- Students propose tasks to include in the simulation
  - Caffeine and alcohol
  - Glucose/insulin dynamics
  - Sleep states
  - Microarrays
  - Surveys

Comput. Biol. Med. Pergamon Press 1973. Vol. 3, pp. 71–78. Printed in Great Britain.

Mathematical Analysis of Blood Glucose and Plasma Insulin Responses to Insulin Infusion in Healthy and Diabetic Subjects*

TADA YIPINTSOI, LAËL C. GATEWOOD, EUGENE ACKERMAN, PATRICIA L. SPIVAK, GEORGE D. MOLNAR, JOHN W. ROSEVEAR and F. JOHN SERVICE†

(*Received* 21 *December* 1971 *and in revised form* 15 *August* 1972)

Abstract—The blood glucose and plasma insulin responses during slow intravenous infusion of insulin in six normal and seven diabetic subjects were fitted to a previously described model utilizing four first-order rate constants for the glucose–insulin interactions. Certain lumped parameters of the model were shown to be characteristic of the subjects' responses and abnormalities. The predicted values of blood glucose and plasma insulin can be made to approximate the actual measurement in all subjects. Additional studies are proposed to delineate further the range of applicability of the model and to characterize diabetic instability.

Blood glucose Mathematical model Diabetes Insulin infusion Computer simulation Optimizing search routine Plasma insulin

THE MATHEMATICAL MODEL

The basic mathematical model used is essentially a deterministic one with two interacting pools, one for blood glucose (G) and the other for the net effective hormone level (H) in the blood. The latter represents a weighted average of all endocrine secretions which tend to alter blood glucose, those which tend to decrease the blood glucose level being considered positive.

A linearized form of this model, which has been shown to be adequate for a variety of tolerance test data,[12] uses the differences (g and h) of G and H, respectively, from their fasting values. The model can be represented analytically by two equations:

$$g' = -m_1 g - m_2 h + J(t)$$

$$h' = -m_3 h + m_4 g + K(t)$$

in which m_1, m_2, m_3 and m_4 are constants characteristic of the individual and J and K are the rates of infusion of exogenous glucose and hormone, respectively.

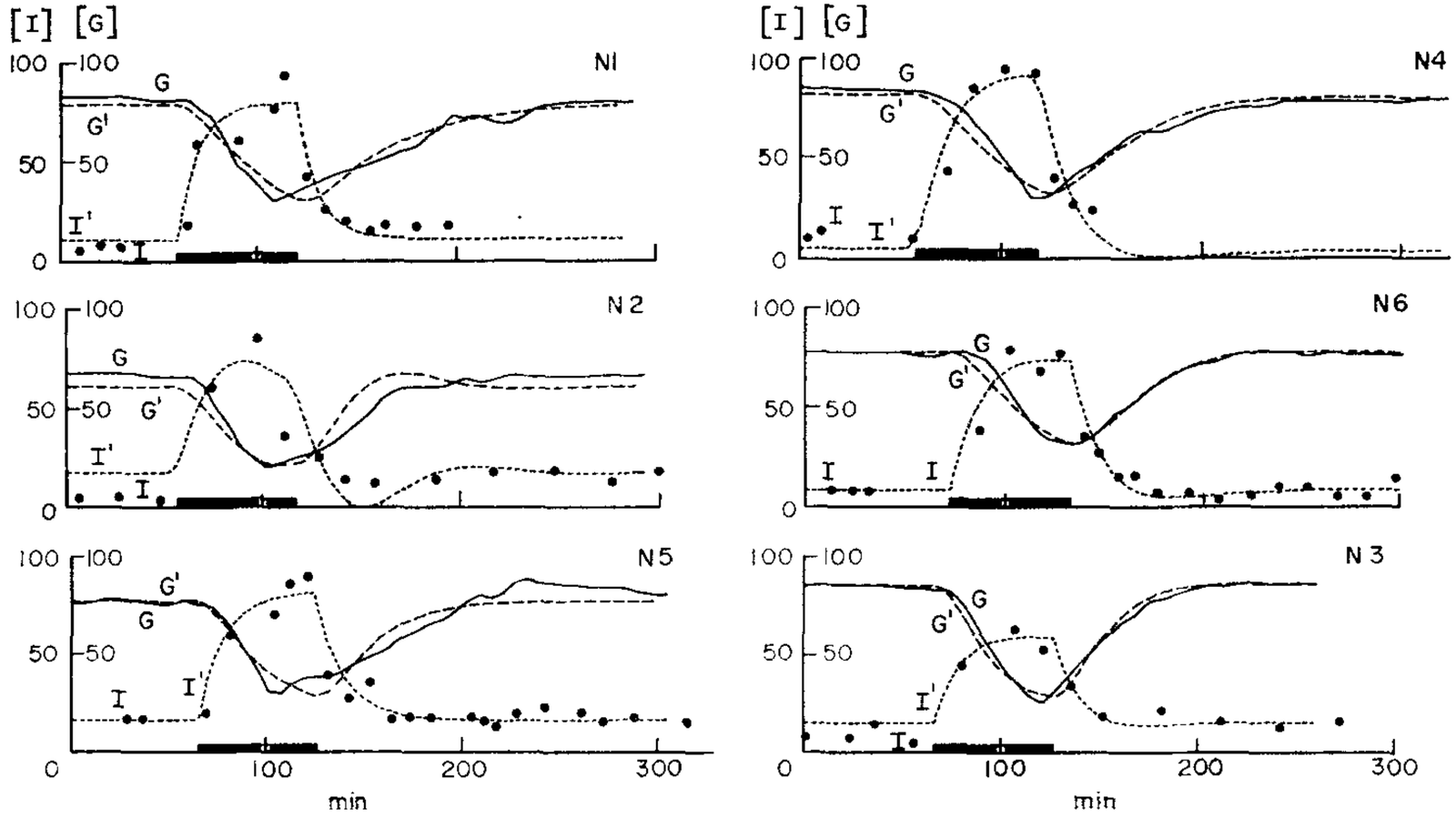


FIG. 1. Simultaneous fitting of both glucose and insulin responses in normal subjects, showing measured glucose (G, continuous lines) and insulin (I, solid circles) and best-fitted glucose (G′, broken lines) and insulin (I′, short-dash lines) responses to slow insulin infusion. Duration of insulin infusion is represented by black bar.

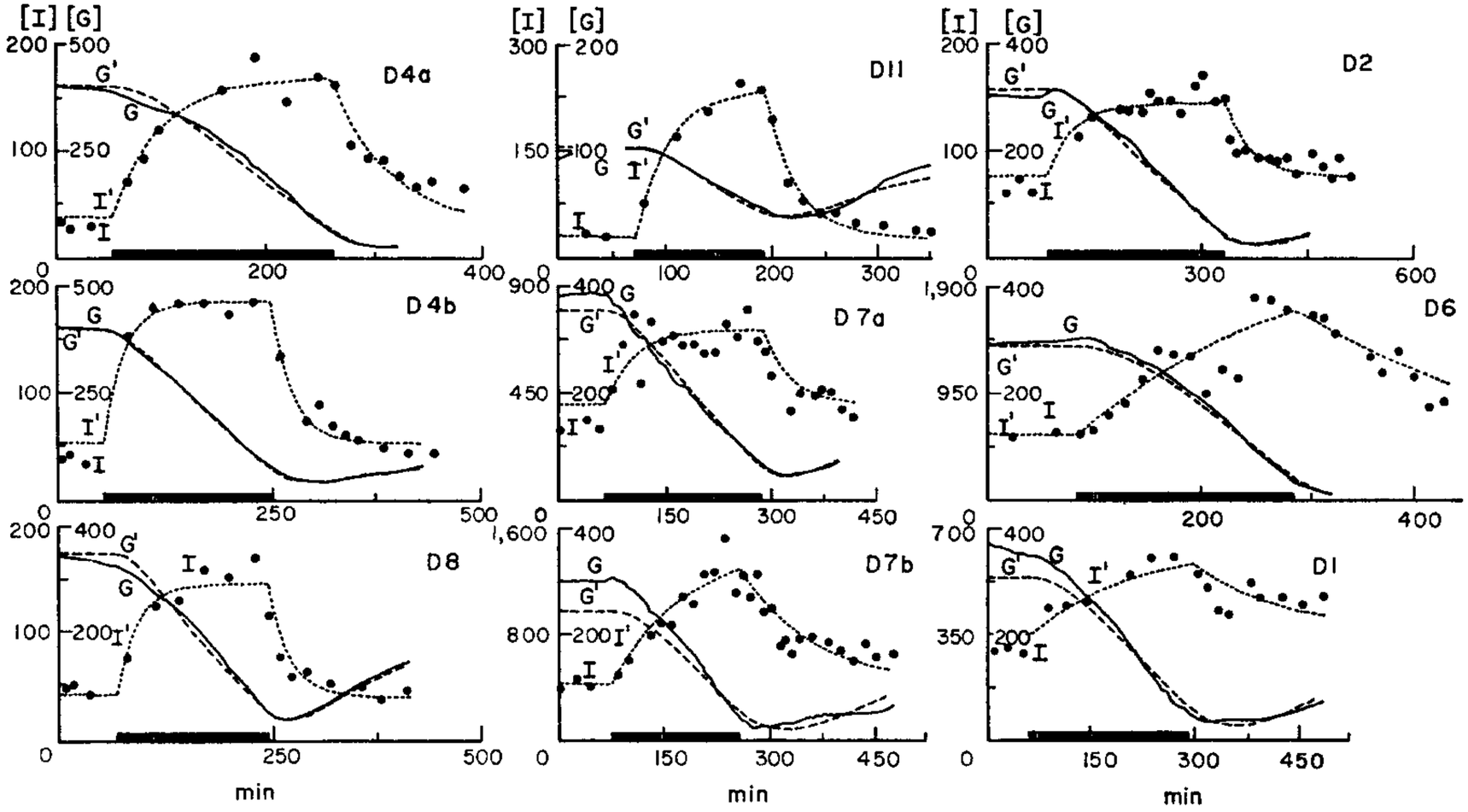


FIG. 2. Simultaneous fitting of both glucose and insulin responses in diabetic subjects. Symbols as in Fig. 1.

TABLE 2. PARAMETERS DERIVED FROM FITTING OF MODEL TO GLUCOSE AND INSULIN RESPONSES

Subject	E_G*	E_H*	ω_0	α	m_1	m_2	m_3	m_4	$2\pi/\omega_0$
N1	0.41	6.5	0.0496	0.0615	0.0251	0.0703	0.0980	0	127
N2	0.65	11.3	0.0649	0.0322	0.0536	0.0858	0.0108	0.0423	97
N5	0.70	2.6	0.0647	0.0651	0.0574	0.1575	0.0729	0	97
N4	0.22	6.5	0.0429	0.0406	0.0273	0.0271	0.0540	0.0136	147
N6	0.09	2.5	0.0508	0.0445	0.0351	0.0262	0.0540	0.0262	124
N3	0.23	1.3	0.0697	0.0604	0.0617	0.0438	0.0590	0.0277	90
D4a	0.15	8.8	0.0067	0.0120	0.0020	0.0014	0.0220	0	942
D4b	0.08	3.9	0.0060	0.0212	0.0009	0.0031	0.0415	0	1057
D8	0.32	13.5	0.0121	0.0227	0.0035	0.0006	0.0418	0	516
D11	0.36	6.9	0.0172	0.0213	0.0088	0.0001	0.0338	0	365
D7a	0.33	364	0.0084	0.0144	0.0027	0.0012	0.0260	0	750
D7b	1.60	442	0.0073	0.0076	0.0056	0.0011	0.0097	0	861
D2	0.11	4.4	0.0068	0.0154	0.0016	0.0143	0.0293	0	925
D6	0.33	939	0.0076	0.0046	0.0081	0.0857	0.0011	0.0006	832
D1	1.10	121	0.0067	0.0067	0.0063	0.0011	0.0072	0	936

Eur J Clin Pharmacol (1983) 24: 93–98

European Journal of Clinical Pharmacology
© Springer-Verlag 1983

The Absolute Bioavailability of Caffeine in Man

J. Blanchard[1] and S. J. A. Sawers[2]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, USA,
and [2]University Department of Therapeutics and Clinical Pharmacology, The Royal Infirmary, Edinburgh, Scotland

Summary. The absolute bioavailability of orally administered caffeine was investigated in 10 healthy adult male volunteers, aged 18.8 to 30.0 years. The subjects were administered a 5 mg/kg dose of caffeine as either an aqueous oral solution or an intravenous infusion, on separate occasions about 1 week apart, in a randomized crossover fashion. Plasma samples were collected over the 24-h period following each dose and assayed for their caffeine content using a high-performance liquid chromatographic

have alluded to the "completeness" of caffeine's absorption following oral administration, they were not designed specifically to answer this question and hence did not utilize a suitable study protocol. The present study was therefore initiated in order to investigate more fully the absorption aspects of caffeine's pharmacokinetics and, in particular, to determine the absolute bioavailability of caffeine administered orally in aqueous solution.

THE EFFECT OF CAFFEINE, COFFEE AND DECAFFEINATED COFFEE UPON BLOOD PRESSURE, PULSE RATE AND SIMPLE REACTION TIME OF MEN OF VARIOUS AGES[1]

KATHRYN HORST AND WILLIAM L. JENKINS

From the Laboratory of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan

Received for publication December 26, 1934

Early investigators (1, 2) found that the simple reaction time of man was decreased under the influence of coffee or caffeine, although more recently (3) an increase has been reported. In these studies the effect of any coffee and tea ingested during the period of experimentation was disregarded. Eddy and Downs (4) found that individuals responded to a very small dose of caffeine by a decrease in reaction time during a period on coffee and by an increase during a period of abstinence. In the present investigation attention was directed toward the duration and the magnitude of the change in reaction time elicited by a single dose of coffee or caffeine. For purposes of control the reaction time after decaffeinated coffee was also studied. Men of various

Journal of Studies on Alcohol, Vol. 42, No.7, 1981

Prediction of Blood Alcohol Concentrations in Human Subjects[1]

Updating the Widmark Equation

Patricia E. Watson, M.H.Sc., Ian D. Watson, Ph.D.
and Richard D. Batt, Ph.D., D.Phil.

SUMMARY. *Equations are derived for expressing the relationship between alcohol intake and blood alcohol concentration in terms of total body water and the blood water fraction. These equations are more exact than Widmark's, and if used in conjunction with regression equations to calculate total body water, will give more accurate predictions of BAC.*

Exploring Mathematical Models for Calculating Blood Alcohol Concentration

S. J. Kouba, M. B. M. Elgindi, R. W. Langer
Department of Mathematics
University of Wisconsin – Eau Claire
Eau Claire, WI 54702-4004

ABSTRACT. A mathematical model for blood alcohol concentration (BAC) that takes into account gender, kidney function, liver function, the amount of alcohol consumed, body weight, and period of alcohol consumption is developed. Graphical results from a Visual Basic program implementing this model agree with the experimental data gathered. Results from this model can be used to inform the public about responsible use of alcohol. It will also allow a person to trace back BAC information to determine the BAC at a time an offense occurred. Finally, accurate determinations of the level and length of time the alcohol remains in the blood are important in studies related to the effects of alcohol on the brain cells and other body organs.

Sleep
9(3):405–414, Raven Press, New York
© 1986, Association of Professional Sleep Societies

Simulation of Human Hypnograms Using a Markov Chain Model

Bob Kemp and Hilbert A. C. Kamphuisen

Department of Clinical Neurophysiology, Academic Hospital Leiden, Leiden, The Netherlands

Summary: A Markov chain model has been proposed as a mechanism that generates human sleep stages. A method for estimating the parameters of the model, i.e., the transition probabilities (rates) between sleep stages, has been introduced and applied to 95 hypnograms taken from 23 subjects. The rates characterize interindividual differences and nightly variations of the sleep mechanism, related to sleep-onset behavior, to the decreasing amount of slow wave sleep in the course of the night, and to the REM-NREM periodicity. The model simulates both probabilistic and the above-mentioned predictable dynamics of sleep, but only if these time-varying, individual rates are applied.
Key Words: Sleep—Models—Estimation—Simulation.

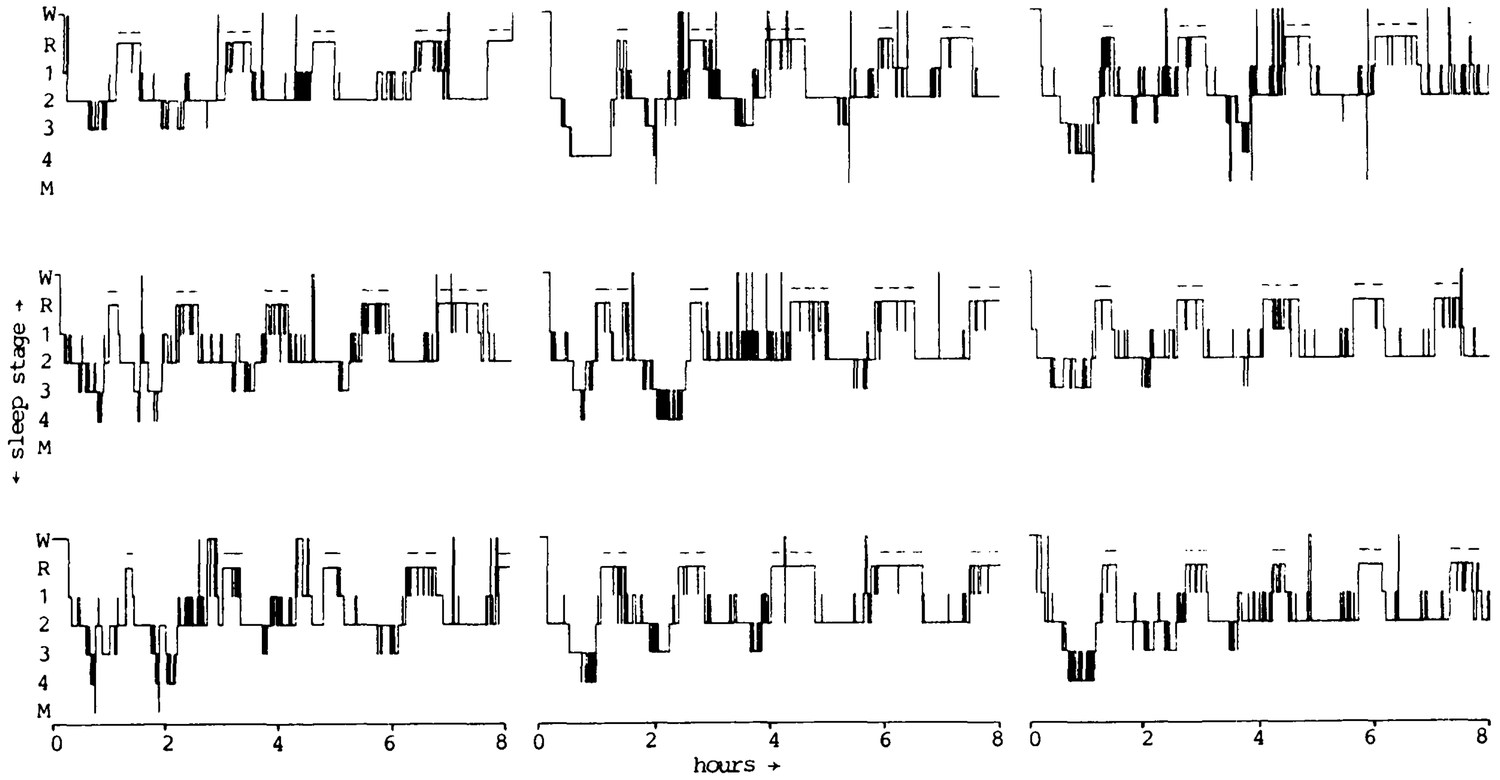


FIG. 1. Hypnograms of 9 nights of subject AD. Lights-off at 0 h. Sleep stages W, wakefulness; R, REM; 1, stage 1; 2, stage 2; 3, stage 3; 4, stage 4; and M, movement time. Note 90-min REM-NREM period and decreasing amount of stages 3 and 4 in the course of the nights. Dashes, REM "blocks."

Journal of Psychopathology and Behavioral Assessment, Vol. 7, No. 3, 1985

A Confirmatory Evaluation of the Profile of Mood States: Convergent and Discriminant Item Validity

John R. Reddon,[1,2] Roger Marceau,[3] and Ronald R. Holden[4]

Accepted: May 16, 1985

The Profile of Mood States was administered to samples of 182 college males, 179 college females, and 257 prison inmates. College males and females did not differ significantly from each other in terms of scale elevation but differed from prison inmates on all scales except Fatigue–Inertia. The college samples differed from the published normative college samples, suggesting the importance of using local norms. A confirmatory item factor analysis suggested convergent item validity with the scoring key and similarity of structure across samples. Discriminant item validity, however, suggested that a smaller number of mood scales would offer a more justifiable interpretation of this inventory.

Table I. Means, Standard Deviations, and Coefficient Alpha Reliabilities

Scale	College males			College females			Prison inmates		
	Mean	SD	Alpha	Mean	SD	Alpha	Mean	SD	Alpha
Tension–Anxiety	8.15	6.02	.87	9.22	6.67	.88	12.47	7.74	.90
Depression–Dejection	8.66	9.80	.93	9.85	9.63	.91	19.84	14.38	.94
Anger–Hostility	7.90	7.95	.91	7.25	8.24	.91	12.33	10.83	.92
Vigor–Activity	18.43	6.33	.89	17.82	6.93	.92	14.89	6.81	.87
Fatigue–Inertia	8.77	6.49	.91	9.46	6.83	.91	8.84	6.67	.90
Confusion–Bewilderment	6.38	4.70	.81	6.54	4.64	.78	8.33	5.83	.82
Total Mood Disturbance	21.45	32.96		24.49	33.51		46.92	42.51	

Journal of Personality and Social Psychology
1998, Vol. 74, No. 4, 865–877

Copyright 1998 by the American Psychological Association, Inc.
0022-3514/98/$3.00

The Relation Between Perception and Behavior, or How to Win a Game of Trivial Pursuit

Ap Dijksterhuis and Ad van Knippenberg
University of Nijmegen

The authors tested and confirmed the hypothesis that priming a stereotype or trait leads to complex overt behavior in line with this activated stereotype or trait. Specifically, 4 experiments established that priming the stereotype of professors or the trait *intelligent* enhanced participants' performance on a scale measuring general knowledge. Also, priming the stereotype of soccer hooligans or the trait *stupid* reduced participants' performance on a general knowledge scale. Results of the experiments revealed (a) that prolonged priming leads to more pronounced behavioral effects and (b) that there is no sign of decay of the effects for at least 15 min. The authors explain their results by claiming that perception has a direct and pervasive impact on overt behavior (cf. J. A. Bargh, M. Chen, & L. Burrows, 1996). Implications for human social behavior are discussed.

Table 1

Experiment 1: Number of Correct Answers (Percentages)

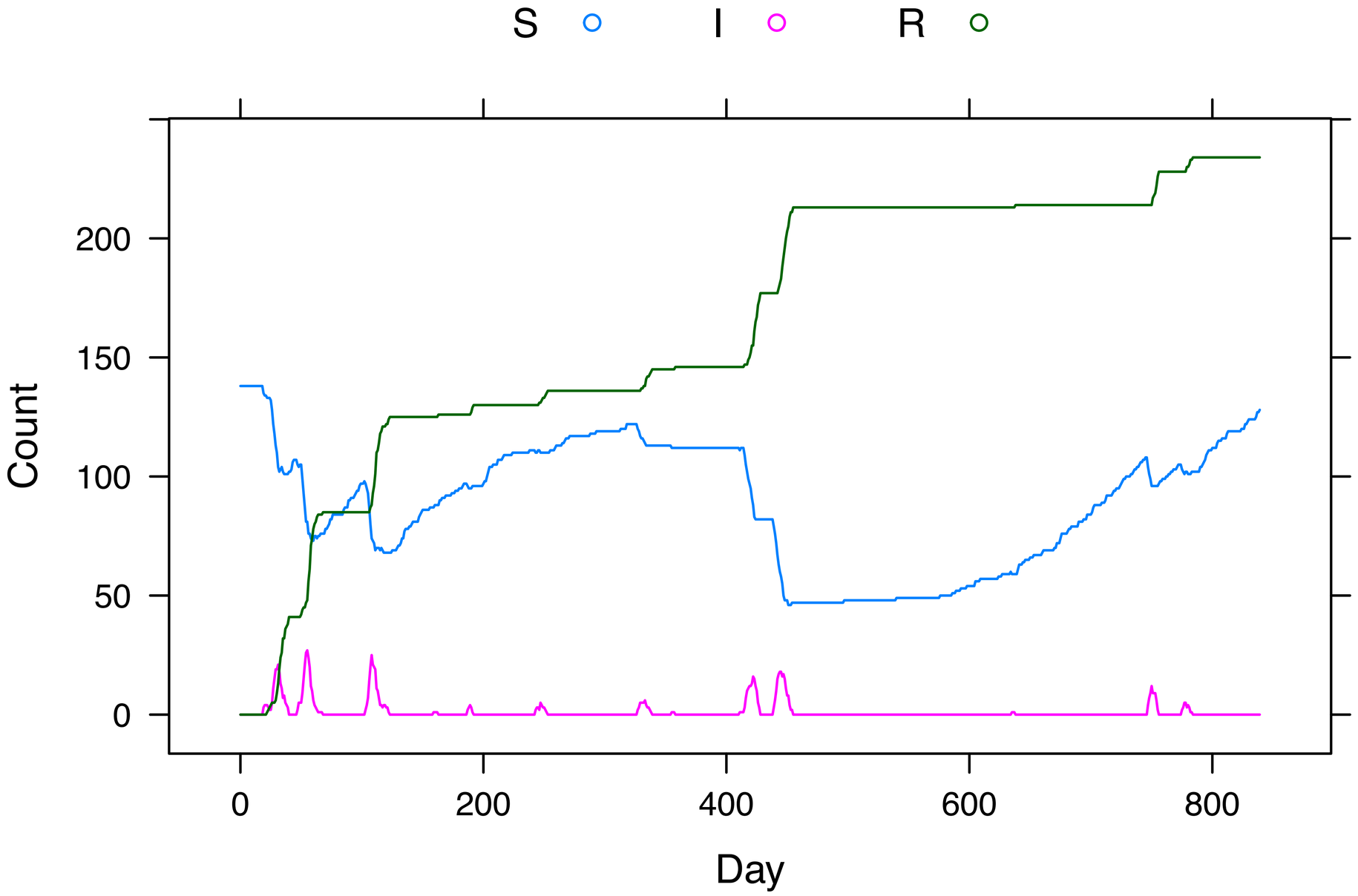
Prime	All questions	Score 1	Score 2	Score 3
No prime	49.9	51.3	46.1	52.3
Professors	59.5	60.0	62.1	56.4
Secretaries	46.4	44.4	46.4	48.4

Current Development

- New models related to
  - Environment and animal populations
  - Education and employment
  - Agricultural production
  - Public health
  - Ethical clearance
- Expand engagement and scope for student projects

Time

- 28 days in the real world is 1 year for the Islanders
- Allows for longitudinal studies and agricultural trials during a semester
- Each week in the real world is then a season for the Islanders
- Physiology still happens in real time (including sleep)


S
I
R
Count
200
150
100
50
0
0
200
400
600
800
Day

Example Project

Genetic Basis of Eye Colour

The participants were randomly selected from the town of Edwardton. All were 6 years of age or older, so that they could complete the survey. The subjects took the survey, which asked for eye colour, then had their combined chromosome mapped onto a microarray. 10 Islanders of each of the 4 eye colours were recruited, for a total of 40 participants. A one-way analysis of variance (ANOVA) test and a Bonferroni correction was used to determine if any genes varied significantly between
eye colour groups.

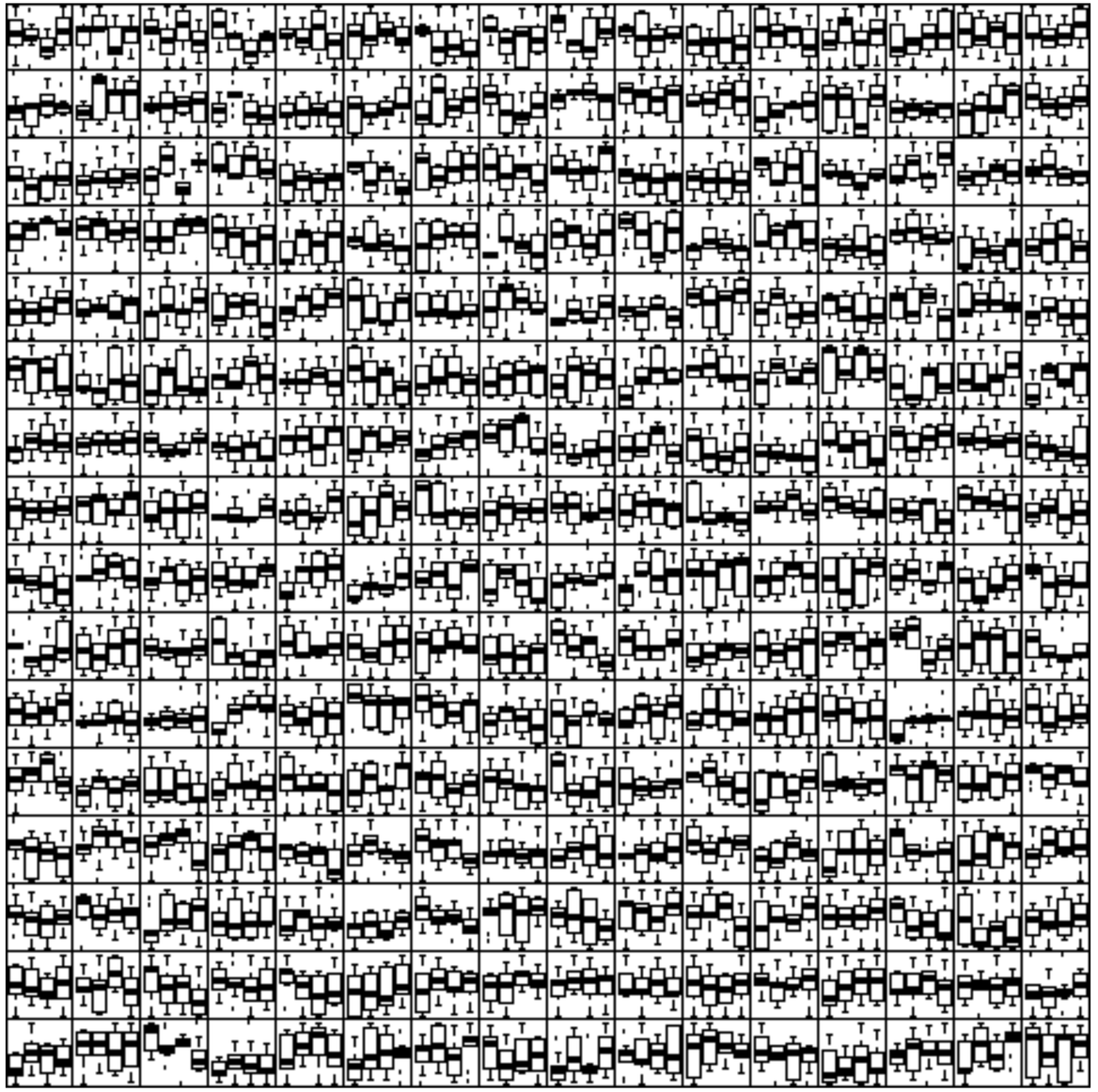


Figure 1. This figure shows side by side box plots of blue, brown, green and purple eye colour, for all 256 Islander genes.

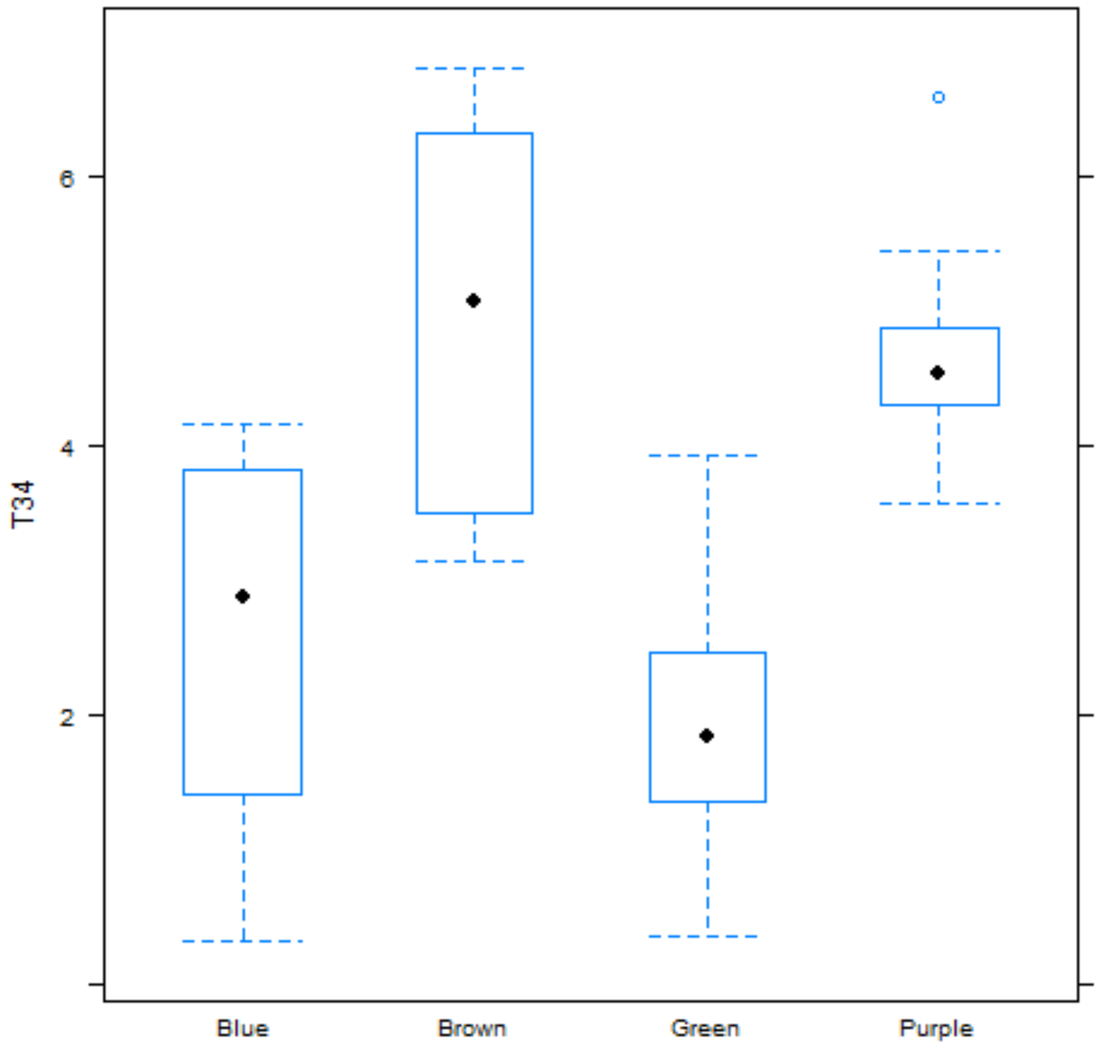


Figure 2. This figure shows side by side box plots for the expression of the T34 gene in the different eye colour groups.

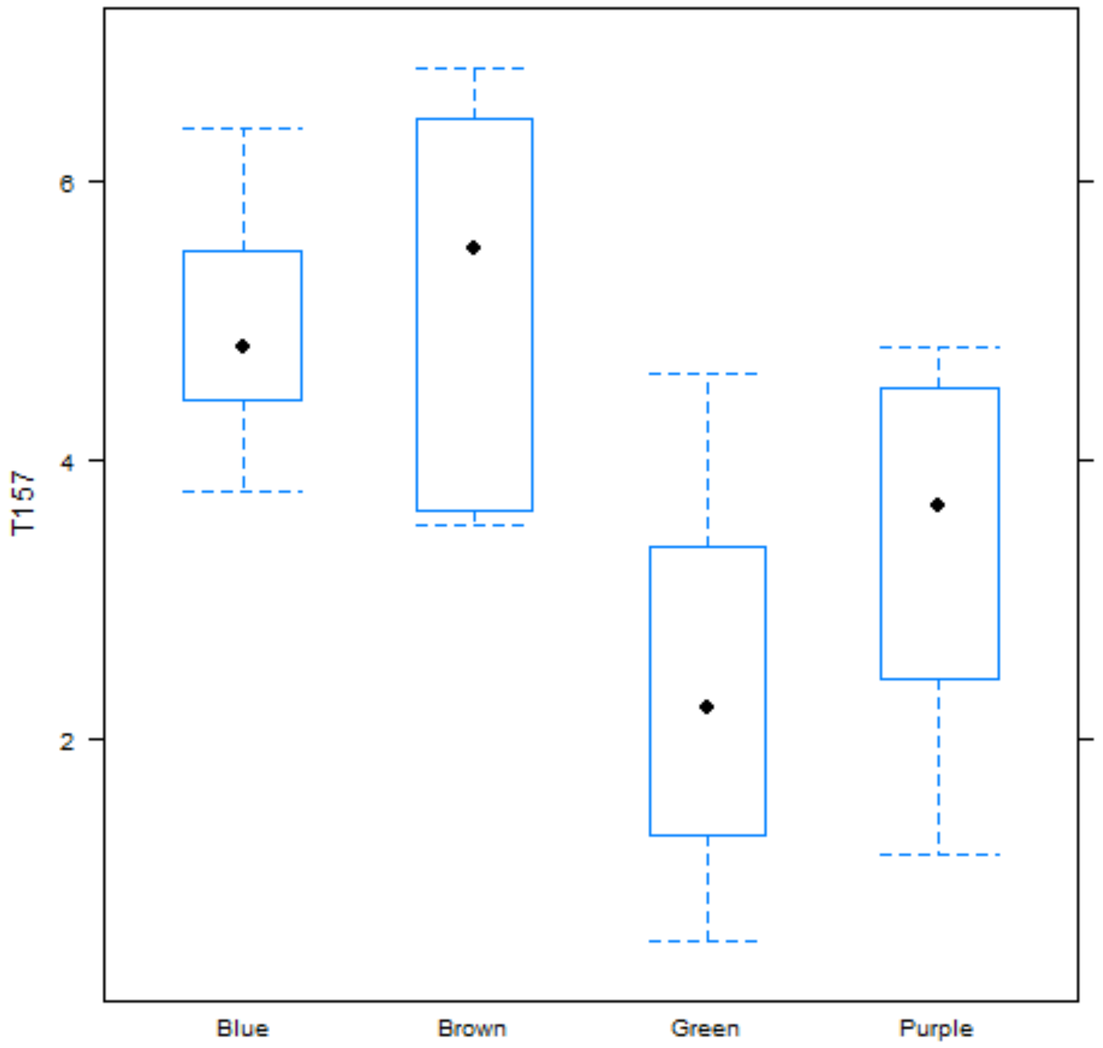


Figure 3. This figure shows side by side box plots for the expression of the T157 gene in the different eye colour groups

Results

The individual boxplots of these two genes, T34 and T157, are shown in Figures 2 and 3… After the Bonferroni correction, the p-values for these genes were 0.0002 and 0.0047 respectively. Figures 2 and 3 suggest that combinations of high and low expression of both genes determine eye colour. It will not however, always be possible to confidently allocate a person's eye colour from the expression of these two genes as there is overlap of the expression of the 4 groups in both genes.

Questions?