State-space models of insulin and glucose responses to diets of varying nutrient content in men and women

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Holtschlag, David J., Mary C. Gannon, and Frank Q. Nuttall. State-space models of insulin and glucose responses to diets of varying nutrient content in men and women. J. Appl. Physiol. 85(3): 935–945, 1998.—Discrete-time state-space models were developed to describe contemporaneous responses of plasma insulin and glucose of normal human subjects. Male and female subjects ingested three consecutive identical meals from isocaloric diets classified as high-carbohydrate, high-fat, high-protein, or standard. Distinctly different glucose and insulin responses were measured in men and women. A seven-state system of linear equations, three in insulin and four in glucose, was identified and estimated to describe responses in men. A six-state system, three in insulin and three in glucose, describes responses in women. Model simulations at 15-min intervals closely match measured concentrations over a 12-h period. Effects of diet content and meal timing on insulin and glucose concentrations were quantified. Dynamic insulin and glucose responses to isocaloric meals of pure carbohydrate, fat, and protein diets were projected on the basis of models developed from mixed diets. The symmetry of the projections indicates that positive excursions in glucose concentrations associated with carbohydrate intake may be matched with negative excursions associated with fat and protein intake to help manage postmeal glucose excursions.

METHODS

Six bivariate series of insulin and glucose concentrations were digitized from average profiles of male and female subjects on high-carbohydrate, -fat, and -protein diets (8). An additional bivariate series resulting from a standard diet for male and female subjects, which was overlaid on each of the insulin and glucose series for high-carbohydrate, -fat, and -protein diets, was also digitized. The bivariate series for the standard diets was used to confirm the accuracy of the digitized records and to further quantify the effects of the three major nutrient components on insulin and glucose concentrations.

Offsets for insulin and glucose concentrations were determined to remove effects of fasting-level concentrations, i.e., baselines, that were unrelated to nutrient intake during the study. Offsets were determined independently for men and women by diet on the basis of prebreakfast measurements. In men, offsets for insulin ranged from 13.2 to 20.4 µU/ml; offsets for glucose ranged from 88.8 to 95.8 mg/dl. In women, offsets for insulin ranged from 11.4 to 15.6 µU/ml; offsets for glucose ranged from 80.6 to 95.1 mg/dl. Deviations from offsets are referred to as excursions or concentrations.

Linear interpolation was used between digitized measurements to obtain 15-min samples within the ~12-h monitoring period for each diet. This sampling interval is longer than the measurement interval during the 1st h after meals, equal to the sampling interval during the 2nd h, and one-half of the sampling interval during the 3rd and 4th h, when fluctuations in insulin and glucose concentrations generally diminished. The 15-min sampling interval was chosen as the shortest, uniform sampling interval that was consistent with the majority of measurement intervals and the local variability in the process dynamics.

Effects of diet content were considered independently, but all diets were analyzed together in a single series for each gender. This ensured that the individual effects associated with carbohydrate, fat, and protein content were estimable and yet that there would be no carryover effects between diets. To accomplish this, the end of each three-meal (12-h) series of 48 samples was extended to 100 time steps by adding one-half of the difference between the previous 15-min value and the offsets. Extended series representing the four diets were concatenated to form two bivariate series of 400 pairs of
insulin and glucose values: one for men and one for women. Offsets for each diet were then removed from each set.

Auxiliary series of diet content and meal timing were formed with the same length as the concatenated bivariate series. The diet content series contained three columns corresponding to the intake of grams per kilogram of body weight of carbohydrates, fats, and proteins, respectively, in any particular meal (Table 1). All food intakes for a particular meal were represented as occurring in a single 15-min interval. The meal timing series was an indicator matrix that consisted of three columns identifying the meal as breakfast, lunch, or dinner by use of a "1" in the appropriate column. All sampling intervals not corresponding to meals contained zeros.

Model conceptualization. The interrelated response of insulin and glucose to dietary intake is complex. These dynamics have been approximated by a variety of techniques, including minimal model analysis (10), extended Kalman filters, and fuzzy filter models (12). The following interrelations were considered in conceptualizing the state-space models developed in this study. Effects of age, activity level, and concentrations of epinephrine, glucagon, glucocorticoids, or growth hormones on insulin and glucose concentrations, however, could not be quantified because of data limitations.

Glucose absorbed after digestion of carbohydrate-containing foods is the major determinant of the postmeal rise in glucose concentrations (5). For most carbohydrate-containing foods, the digestion rate exceeds the glucose absorption rate. Quantitatively, the amount of galactose present in the diet is not metabolically significant. The amount of fructose absorbed is significant, but it results in little rise in plasma glucose concentration. In comparison to carbohydrate, ingested protein has little effect on the blood glucose concentration or on digestion and absorption of monosaccharides (6). Ingested fat may affect the rate of digestion of carbohydrate and the absorption of monosaccharides, but the effect is delayed and becomes progressively more prominent with the second and third meals throughout the day (8).

Glucose and fructose are absorbed from dietary sources, as well as protein, stimulates insulin secretion. Ingested fat also may potentiate the amounts of insulin stimulated by ingested carbohydrates. The effect of these ingested nutrients on insulin secretion is direct, through stimulation of insulin secretion (via glucose and absorbed amino acids), and is indirect, through stimulation of incretin hormone secretion (via ingested proteins, carbohydrates, and fats). Ingested protein and fructose stimulate glucagon secretion. Glucagon secretion is inhibited by glucose-containing foods. Glucagon stimulates glucose release by the liver. Insulin inhibits glucose release by the liver. The net effect on glucose production, therefore, depends on the ratio of glucagon to insulin. Glucagon does not affect insulin-stimulated uptake and storage of glucose in skeletal muscle.

The mathematical model conceptualized in this study is a simplified, linear, time-invariant approximation to the complex dynamics between insulin, glucose, and nutrient intake. Simplifications were necessary because of uncertainties in physical processes and limitations of available data. These limitations restrict application of the model to prediction of short-term (4-h) effects within the range of dietary conditions represented by the data. The 15-min sampling interval further restricts the resolution of the temporal dynamics. Finally, circadian variations in these dynamics, associated with variations in activity or other factors, are approximated only by meal-timing effects. Despite these limitations, the model is intended for simulation of postmeal insulin and glucose excursions with sufficient accuracy to identify primary effects of dietary content and meal timing and to aid in the management of glucose concentrations.

Model formulation. The dynamic response of insulin and glucose to nutrient intake was formulated as a discrete-time, state-space model (4, 9). This model contains two equations: a state equation and an observation equation. The state equation describes the dynamics of the process at time steps indexed by \(k+1\) on the basis of information available at and before time \(k\). The length of the state vector is determined by the order of the difference equations (number of delays of the response variables) needed to adequately describe the process dynamics. The observation equation transforms the state vector by reducing the dimension to the number of attributes measured at the process at time \(k\). The innovations form, which includes estimation of the \(K\) matrix below, of the state-space model was selected to help ensure that the model errors (innovation sequences) were uncorrelated. Uncorrelated innovation sequences simplify testing of the statistical significance of estimated model parameters. Also, the innovations form is convenient for real-time estimation of error-corrected predictions of insulin and glucose. The innovations form of the state-space equation is expressed as

\[
x(k + 1) = A(x) \cdot x(k) + B(u) \cdot u(k) + K(e) \cdot e(k)
\]

where \(x(k + 1)\) is a column vector sequence of length \(n\) representing the state of the system at time indexed by \(k+1\). The order of the state vector, \(n\), is the sum of the orders \(n_1\) and \(n_2\) needed to simultaneously describe interacting insulin \(n_1\) and glucose \(n_2\) excursions. The index \(k\) identifies discrete time steps separated by 15-min intervals. The initial state \((k = 0)\) was a zero vector.

\(A(x)\) is an \(n\) (row)-by-\(n\) (column) matrix of coefficients and parameters relating the state at time \(k\) to the state at time \(k+1\). Coefficients refer to structural elements of the \(A\) matrix, whereas parameters refer to elements that are adjusted so that simulated concentrations match measured concentrations.

\(B(u)\) is an \(n\)-by-\(r\) matrix of parameters relating the effect of diet and meal timing, \(u(k)\), to the state vector. The dimension \(r\) is the number of columns in the forcing function \(u\) matrix.

\(u(k)\) is an \(r\) row vector sequence containing values of the forcing function. In this analysis, \(r\) was equal to 6, corresponding to the amounts of carbohydrate, protein, and fat (diet content) ingested at time \(k\) and three separate column indicators for breakfast, lunch, and dinner (meal timing).

\(K(e)\) is an \(n\)-by-\(2\) matrix of parameters relating the innovations at time \(k\), \(e(k)\), to the state at \(k + 1\).

\(e(k)\) is a two-row vector sequence of innovations (errors) between model estimates and measured values of insulin and glucose at time \(k\).
y(k) is a two-row vector sequence of measured excursions in insulin and glucose. 

C is a 2-by-n matrix of coefficients used to extract simulated insulin and glucose concentrations from the state vector.

Model identification and estimation. Model identification determines the minimum model order (number of delays of the response variables) needed to adequately describe the process dynamics. In this analysis, alternate models between second and fourth order were evaluated for male and female data sets. Given the similarity of the insulin and glucose profiles, only models for insulin and glucose that differed by one order or less were evaluated.

The primary criterion used to select model order was the minimization of Akaike’s final prediction error (FPE) (3). The FPE provides a measure for comparing alternate models on the same data set by adjusting the loss function, computed as the determinant of the innovations matrix, to account for different numbers of parameters among models. The adjustment compensates for a tendency to have an automatic decrease in the loss function with an increase in the number of parameters. In cases where the FPE contained more than one local minimum for various model orders, the minimum model order was chosen that was consistent with the data.

Once the model order was determined, estimates were computed for the parameters A, B, and K in the state-space equation. Parameter estimates were computed by use of a robustified quadratic prediction-error criterion minimized using an iterative Gauss-Newton algorithm (3). A stability test of the model was performed to ensure that only models corresponding to stable predictors were estimated. Finally, the statistical significance of each parameter was evaluated on the basis of a Student’s t-test. Those parameters that were not significantly different from zero were set to zero, and if the system was stable under those initial parameter conditions, the system was reestimated. If the FPE of the reestimated system was lower after elimination of the parameter, the simpler model was retained. This procedure was repeated until no additional parameters could be eliminated.

RESULTS

Insulin and glucose dynamics in men. A coupled third-order insulin model and a fourth-order glucose model were selected for the male series on the basis of the FPE criteria (Table 2). Elimination of insignificant parameters A(7,1) and A(7,2) and B(1,1), B(1,2), and B(5,6) reduced the FPE of the male model from 93.44 to 75.93. The estimated state equation for men is

\[ x(k - 1) = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0.41\# & -1.09\# & 1.62\# & -0.69\# & 1.81\# & -2.42\# & 1.48\# \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0^* & 0^* & 0.0014\# & -0.28\# & 0.94\# & -1.84\# & 2.17\# \end{bmatrix} u(k) + \begin{bmatrix} x(k - 2) \\ x(k - 1) \\ x(k) \\ x_g(k - 3) \\ x_g(k - 2) \\ x_g(k - 1) \\ x_g(k) \end{bmatrix} + \cdot \cdot \cdot \]

\[ \begin{bmatrix} 0^* & 0^* & -12.66\# & 42.01\# & 47.91\# & 50.16\# \\ -40.27\# & -36.80\# & -93.68\# & 427.5\# & 435.6\# & 427.8\# \\ -76.24\# & -72.17\# & -151.1\# & 727.8\# & 720.8\# & 714.8\# \\ 74.27\# & 58.99\# & 111.5\# & -551.4\# & -555.5\# & -556.9\# \\ 9.12\# & 1.35 & -5.06\# & 10.53\# & 7.34\# & 0^* \\ -63.14\# & -62.76\# & -123.5\# & 590.6\# & 587.9\# & 582.7\# \\ -60.70\# & -59.78 & -113.6\# & 547.0\# & 546.8\# & 545.0\# \end{bmatrix} \cdot e(k) \]

\[ \begin{bmatrix} 0.63\# & -0.16 \\ 0.35\# & -0.12 \\ 0.13\# & -0.39\# \\ -0.08\# & 0.85\# \\ -0.13\# & 0.55\# \\ -0.21 & 0.25\# \\ -0.21 & 0.21\# \end{bmatrix} \]

\[ C = \begin{bmatrix} 0.08\# & 0.94\# \\ 0.21 & 0.94\# \\ 0.63 & 0.35\# \\ 0.35 & 0.13\# \\ 0.21 & 0.13\# \\ 0.21 & 0.21\# \end{bmatrix} \]

\[ \begin{bmatrix} 0^* & 0^* & 0.0014\# & -0.28\# & 0.94\# & -1.84\# & 2.17\# \end{bmatrix} \]

\[
\begin{array}{c}
0^* \\
-12.66\# \\
42.01\# \\
47.91\# \\
50.16\# \\
-40.27\# \\
-36.80\# \\
-93.68\# \\
427.5\# \\
435.6\# \\
427.8\# \\
-76.24\# \\
-72.17\# \\
-151.1\# \\
727.8\# \\
720.8\# \\
714.8\# \\
74.27\# \\
58.99\# \\
111.5\# \\
-551.4\# \\
-555.5\# \\
-556.9\# \\
9.12\# \\
1.35 \\
-5.06\# \\
10.53\# \\
7.34\# \\
0^* \\
-63.14\# \\
-62.76\# \\
-123.5\# \\
590.6\# \\
587.9\# \\
582.7\# \\
-60.70\# \\
-59.78 \\
-113.6\# \\
547.0\# \\
546.8\# \\
545.0\#
\end{array}
\]

where * indicates that the parameter was set to zero without significantly degrading model performance on the basis of the FPE criteria; some parameters were not significantly different from zero but could not be eliminated, because stable initial parameter values could

\[ 1 \text{ The robust estimation technique limited the influence of large individual prediction errors on parameter estimates. Specifically, prediction errors that were } > 1.6 \text{ times the estimated standard deviation of the innovations sequence, } \epsilon(k), \text{ carried a linear, rather than a quadratic, weight.} \]

\[ 2 \text{ Elements in matrices are identified by their row and column indexes. Thus } A(1,2) \text{ refers to the element in matrix } A \text{ in row } 1 \text{ (top row) and column } 2 \text{ (from the left). Furthermore, a colon is sometimes used to represent a sequence, so that } A(1:4,5:7) \text{ indicates a } 4 \times 3 \text{ submatrix of } A \text{ consisting of rows } 1-4 \text{ and columns } 5-7. \text{ Finally, a colon shown by itself indicates all rows or columns depending on its position with respect to the comma separating row and column indexes.} \]
Finally, the covariance of innovations describes the variance of the errors in insulin and glucose estimates on the diagonal terms and covariance between model error sequences on the equal, off-diagonal terms. For the model developed for men, the covariance of the innovations is

$$\text{Var}(e) = \begin{bmatrix} 14.60 & 3.53 \\ 3.53 & 4.61 \end{bmatrix}$$

The innovation sequences were not significantly auto- or cross-correlated.

### Table 2. Relation between model selection criteria and model order

<table>
<thead>
<tr>
<th>Model Order</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insulin</td>
<td>Loss function FPE</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>139.7</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>165.4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>168.3</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>84.44</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>65.84</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>66.81</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>67.68</td>
</tr>
</tbody>
</table>

Boldface values identify selected model orders and final prediction error (FPE).

Model parameters provide some information on the process being simulated. Elimination of elements $A(7,1)$ and $A(7,2)$ and the relatively small magnitude (and significance) of element $A(7,3)$ indicate a relatively small marginal effect (unaccounted for other dynamics or food inputs) of past insulin concentrations on future glucose concentrations. In contrast, the significance of elements $A(3,4:7)$ indicates that past glucose concentrations have a significant effect on future insulin concentrations.

The $B$ matrix indicates the relative effects of nutrient components, $B(:,1:3)$, and meal timings, $B(:,4:6)$. In general, the signs of these two sets of parameters are opposite for each element in the state vector for the insulin components, $B(1:3,:)$, and the glucose components, $B(1:4,:)$. For example, parameters $B(3,1:3)$ are all negative and parameters $B(3,4:6)$ are all positive, whereas parameters $B(4,1:3)$ are all positive and parameters $B(4,4:6)$ are all negative. Interrelations among the magnitudes of parameters in the $B$ matrix provide differentiation among effects associated with nutrient components and meal timings.

A sampled and a continuous representation of simulated excursions of insulin and glucose in men in response to standard, high-carbohydrate, high-fat, and high-protein diets are shown on Fig. 1. High-carbohydrate and standard diets create similar abrupt increases in insulin and glucose concentrations for all meals. In contrast, distinct effects of meals on insulin or glucose concentrations are seen in response to high-fat and high-protein diets.

### Table 3. Summary of simulated values and model errors during 4-h periods after meals

<table>
<thead>
<tr>
<th>Diet content</th>
<th>Men Insulin</th>
<th>Women Insulin</th>
<th>Men Glucose</th>
<th>Women Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>SEM</td>
<td>R</td>
<td>Bias</td>
</tr>
<tr>
<td>High CHO</td>
<td>-0.15</td>
<td>1.10</td>
<td>0.93</td>
<td>-0.94</td>
</tr>
<tr>
<td>High fat</td>
<td>0.12</td>
<td>0.79</td>
<td>0.63</td>
<td>-0.49</td>
</tr>
<tr>
<td>High protein</td>
<td><strong>2.22</strong></td>
<td><strong>0.98</strong></td>
<td>0.88</td>
<td>0.17</td>
</tr>
<tr>
<td>Standard</td>
<td>1.08</td>
<td>1.05</td>
<td>0.93</td>
<td>-0.19</td>
</tr>
<tr>
<td>Meal timing</td>
<td>Breakfast</td>
<td>1.36</td>
<td>0.90</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>Lunch</td>
<td>0.05</td>
<td>0.66</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Dinner</td>
<td>1.04</td>
<td>0.98</td>
<td>0.91</td>
</tr>
</tbody>
</table>

SEM, standard error of mean (bias); R, sample linear correlation coefficient between simulated and interpolated (observed) values. Pairs of boldface bias and SEM terms identify significantly biased estimates.

Not be established; † indicates an apparent significance at the 0.05 probability level; and ‡ indicates an apparent parameter significance at the 0.01 probability level.
Fig. 1. Insulin and glucose response of men to isocaloric diets high in carbohydrate, fat, or protein. Solid line, modeled values; ○, interpolated values; +, digitized values. Vertical bars, meal timing (breakfast (B), lunch (L), and dinner (D)).
glucose excursions are less apparent from the high-fat diet. High-protein diets are associated with minor glucose excursions; however, distinct increases in insulin concentrations are apparent for all meals.

In general, model-simulated values correspond closely to sampled values. The simulated values differ from an explicit application of the male state-space model in that no error correction was involved \([K(i) = 0]\). Inclusion of error-correction components, e.g., computation of one-step-ahead predicted values, would have resulted in a smaller discrepancy between sampled and simulated values. However, error correction would have made determination of the effects of diet content and meal timing on insulin and glucose excursions more difficult.

Results of an analysis of simulated values and model errors during 4-h periods after each meal are shown in Table 3. For insulin and glucose, sampled and simulated values are highly correlated \((R > 0.92)\) for the high-carbohydrate and standard diets. Sampled and simulated insulin and glucose concentrations have the lowest correlation for high-fat diets, although the excursions (and the standard errors of the bias) in insulin and glucose concentrations are also least for the high-fat diet. For the high-protein diet, insulin concentrations are somewhat underestimated and glucose concentrations are overestimated. These biases are likely the result of the generally diminished correlation between insulin and glucose excursions that is unique to the high-protein diet. Finally, simulated glucose excursions overestimate sampled values for men after breakfast. Some of the model error may be attributable to differences in glycemic effects of foods in the various diets (7, 11, 13).

Insulin and glucose dynamics in women. The identified female model is a coupled third-order system in insulin and glucose (Table 2). Elimination of insignificant parameters \([B(4,5)\) and \(K(6,1)\) from the full model reduced the FPE of the female model from 153.2 to 128.3. The estimated state equation for women is

\[
\begin{bmatrix}
  x_1(k - 1) \\
  x_2(k) \\
  x_3(k + 1) \\
  x_4(k - 1) \\
  x_5(k) \\
  x_6(k + 1)
\end{bmatrix} =
\begin{bmatrix}
  0 & 1 & 0 & 0 & 0 & 0 \\
  0 & 0 & 1 & 0 & 0 & 0 \\
  -1.63\dagger & 2.77\dagger & -0.16 & 2.75\dagger & -7.08\dagger & 4.45\dagger \\
  0 & 0 & 0 & 0 & 1 & 0 \\
  0 & 0 & 0 & 0 & 0 & 1 \\
  -0.93\dagger & 2.08\dagger & -1.16\dagger & 1.48\dagger & -4.48\dagger & 4.04\dagger \\
\end{bmatrix}
\begin{bmatrix}
  x_1(k - 2) \\
  x_2(k - 1) \\
  x_3(k) \\
  x_4(k - 2) \\
  x_5(k - 1) \\
  x_6(k)
\end{bmatrix}
+ \cdots +
\begin{bmatrix}
  -31.32\dagger & -27.56\dagger & -56.78\dagger & 281.6\dagger & 277.6\dagger & 276.8\dagger \\
  -112.4\dagger & -103.8\dagger & -207.7\dagger & 1021\dagger & 1004\dagger & 1003\dagger \\
  -31.49\dagger & -37.94\dagger & -70.89\dagger & 378.0\dagger & 349.4\dagger & 354.7\dagger \\
  -2.76\dagger & -1.22\dagger & -1.98\dagger & -0.89\dagger & 0^* & -1.28\dagger \\
  -8.25\dagger & -13.94\dagger & -28.44\dagger & 134.3\dagger & 132.3\dagger & 131.5\dagger \\
  55.43\dagger & 38.72\dagger & 79.96\dagger & -383.8\dagger & -386.0\dagger & -383.5\dagger \\
\end{bmatrix}
\begin{bmatrix}
  u(k) \\
  e(k)
\end{bmatrix}
\begin{bmatrix}
  0.55\dagger & 0.09 \\
  0.42\dagger & 0.19\dagger \\
  0.31\dagger & -0.14 \dagger \\
  0.12\dagger & 0.68\dagger \\
  0.05\dagger & 0.37\dagger \\
  0^* & 0.03
\end{bmatrix}
\]

where *, †, and ‡ are as described in Table 2. The observation equation for women is

\[
y(k) =
\begin{bmatrix}
  1 & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & 1 & 0 & 0 & 0 \\
  x_1(k + 1) \\
  x_2(k - 1) \\
  x_3(k) \\
  x_4(k + 1)
\end{bmatrix}
+ e(k)
\]

Finally, the covariance of the innovations sequence is

\[
\text{Var}(e) =
\begin{bmatrix}
  11.41 & 1.96 \\
  1.96 & 8.76
\end{bmatrix}
\]

Again, as in the male model, the innovation sequences were not significantly temporally or intercorrelated.

In women, insulin excursions are strongly influenced by second-order dynamics given the large magnitude of the parameter associated with insulin at time \(k - 1\) \([A(3,2) = 2.77]\) relative to the parameter at time \(k\) \([A(3,3) = -0.16]\). This characteristic may help explain the slower, smoother responses of insulin and glucose in women than in men. Predicted insulin concentra-
tions (at \(k + 1\)) are positively associated with glucose values at time \(k\), as indicated by \(A(3,6) = 4.45\). Predicted glucose values are negatively associated with values of insulin at time \(k\), as indicated by \(A(3,3) = -1.16\), and positively associated with values of glucose at time \(k\), as indicated by \(A(6,6) = 4.04\).

As in the case for men, the signs of the two sets of parameters in the \(B\) matrix corresponding to the...
Insulin components, \( B(:,1:3) \), and the glucose components, \( B(:,4:6) \), are generally opposite for each element in the state vector. For example, parameters \( B(3,1:3) \) are all negative and parameters \( B(3,4:6) \) are all positive, whereas parameters \( B(6,1:3) \) are all positive and parameters \( B(6,4:6) \) are all negative. Here also, interrelations among the magnitudes of parameters in the \( B \) matrix provide differentiation among effects associated with nutritional components and meal timings.

Sampled and simulated excursions of insulin and glucose in women responding to standard, high-carbohydrate, high-fat, and high-protein diets are shown in Fig. 2. Insulin and glucose excursions have a lower, narrower peak for the standard diet than for the
corresponding high-carbohydrate diet. High-carbohydrate diets resulted in the greatest excursions in insulin and glucose; however, the peaks were distinctly broader and generally had slower responses than corresponding responses in men. Also, in contrast to men, insulin and glucose responses in women to high-fat diets were distinct for each meal, with a peak in the response after breakfast almost twice that after lunch or dinner. Female responses were similar to the male responses for the high-protein diet. Both sets showed distinctly elevated insulin concentrations but only minor excursions in glucose. Insulin and glucose excursions have a lower, narrower peak for the standard diet than for the corresponding high-carbohydrate diet.

Fig. 4. Projected insulin and glucose response of women to isocaloric diets of pure carbohydrate, fat, or protein. See Fig. 3 legend for explanation of symbols. All responses converged to zero.
Results of an analysis of simulated values and model errors during the 4-h periods after each meal are shown in Table 3. For insulin and glucose, sampled and simulated values are highly correlated (R > 0.96) for the high-carbohydrate diet. Sampled and simulated insulin concentrations have the lowest correlation (R = 0.786) for the high-fat diet. No biases were detected with respect to diet contents or meal timings in the female responses.

**DISCUSSION**

Insulin and glucose excursions were projected (extrapolated) to depict the male and female responses to diets of pure carbohydrate, fat, and protein by use of the linear state-space models (Figs. 3 and 4). The projections are based on isocaloric meals of 38 cal/kg body wt of pure carbohydrate, fat, and proteins. By use of data in Table 1, the calories per gram of carbohydrate, fat, and protein were computed as 3.815, 8.546, and 4.563, respectively. Thus nutrient inputs to the state-space model for projection of responses to pure carbohydrate, fat, and protein diets were 9.961, 4.447, and 8.328 g/kg body wt, respectively.

In men, projected insulin excursions resulting from carbohydrate and fat track projected glucose excursions. That is, positive (negative) excursions in glucose are contemporaneously associated with positive (negative) excursions in insulin. In women, projected insulin concentrations decrease immediately after carbohydrate ingestion, perhaps because the short-term increase in insulin production is delayed or is not sufficient to offset increased requirements associated with the increased production of glucose. In contrast, the projected insulin response to fat ingestion in women apparently exceeds the short-term requirements, resulting in a positive excursion in insulin and predominantly negative excursion in glucose. Positive insulin excursions are associated with protein ingestion in men and women; corresponding glucose excursions are predominantly negative. Differences among projected re-
responses for breakfast, lunch, and dinner were minor (Figs. 3 and 4).

A continuous representation of the discrete-time initial-condition responses for insulin and glucose in men and women is shown in Fig. 5. Figure 5 (top) shows the responses of initially elevated insulin concentrations (100 µU/ml) and base-level glucose concentrations (zero). Similarly, Fig. 5 (bottom) shows the responses of initially elevated glucose concentrations (100 mg/dl) and base-level insulin concentrations. The simulated initial-condition responses in men and women are conditionally stable, because all concentrations tend to zero with increasing time. In addition, the initial-condition responses to elevated insulin concentrations and the male response to elevated glucose concentrations monotonically tend to zero, indicating unconditional stability. However, the slight rise in female glucose concentrations for the elevated glucose simulation indicates that the stability of the glucose response is dependent on the insulin concentration. Therefore, this simulated response is not unconditionally stable. Further investigation is needed to determine a stable parameterization.

Despite this limitation of the female model, two patterns are consistent in the male and female models. First, elevated insulin concentrations lower glucose concentrations. This simulated effect is consistent with insulin's role in inhibiting production of glucose and in stimulating the removal of glucose from circulation. Second, elevated glucose concentrations raise insulin concentrations. This simulated effect is consistent with the stimulation of insulin produced by a rise in glucose and gut hormone-mediated release of insulin secretion (7).

The model may be extended to facilitate real-time control of glucose excursions in people with insulin-requiring diabetes. Extension will necessitate a reformulation of the model to simultaneously predict plasma glucose concentrations and insulin effectiveness as a function of dietary inputs, insulin dosage, and motor activity levels. This extension will necessitate additional clinical study involving people with insulin-requiring diabetes, in which heart rate, perhaps, is monitored as a measure of motor activity, with consideration of possible confounding factors such as insulin absorption rates and insulin injection sites.

A Kalman filter (1) implementation of the state-space equations may facilitate real-time glycemic control by supplementing information on model estimates with information on model uncertainties. Augmenting the state vector with data on other hormone concentrations, particularly glucagon, may help refine model simulations of insulin and glucose dynamics. Results from future model studies may be applied to a larger population if subjects from more than one age group are included in clinical studies.

In summary, linear state-space models provide an effective mechanism for simulating the short-term (4-h), contemporaneous response of insulin and glucose to isocaloric meals for a wide range of nutrient contents. These models describe the dynamic characteristics of insulin and glucose responses with sufficient accuracy to identify primary effects associated with specific dietary content and meal timing. Separate models are needed to accurately describe the distinct dynamic characteristics of responses in men and women. Some model error is thought to be associated with variation in the glycemic effect of selected dietary components and with circadian variations in subject activity and hormone concentrations.

Responses of insulin and glucose to pure carbohydrate, fat, and protein can be projected from data on meals of mixed nutrient composition. In this study, projections for men and women indicate that glucose concentrations rise after ingestion of pure carbohydrates and generally fall after ingestion of pure fat and protein. The symmetry of the projected responses with time indicates that state-space models may be useful for designing the nutrient composition of meals to manage plasma glucose excursions. In addition, the simulated glucose response in nondiabetics may provide a reference concentration sequence for control of glucose excursions in diabetic patients requiring insulin, once a continuous, portable glucose-monitoring device is available. Additional research is needed to extend the model applicability to a wide range of caloric intakes and a wider variety of foods than were available in this investigation.

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REFERENCES