Multivariate Statistical Monitoring Strategy for an Artificial Pancreas Application

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Type 1 Diabetes Mellitus

- Auto-immune disease
- Insufficient insulin secretion by the pancreatic β-cells
- Inadequate regulation of blood glucose (*glycemia*)
  - High glucose levels (*hyperglycemia*): long-term health complications (e.g., eye, nerve, and kidney disease)
  - Low glucose levels (*hypoglycemia*): immediate health risks (e.g., insulin shock)
- Treatment: finger sticks, insulin therapy, constant decision-making

Insulin Therapy

- Exogenous insulin required for survival
  - Delivered through multiple daily injections or a subcutaneous insulin infusion pump
    - *Basal:* Steady rate of infusion in fasting states
    - *Bolus:* Large injection to offset effects of the carbohydrate (CHO) content of a meal

- Requires constant decision-making by patients and their caregivers
  - Occasional basal adjustments
  - Estimation of CHO in meals ("carb counting") and consequent bolus amount
  - Correction bolus or meal

Ultimate Goal: "Artificial Pancreas"

- Medical device which automatically regulates glycemia and frees diabetes patients from onerous daily self management
  - Continuous glucose sensor
  - Insulin infusion pump
  - Feedback/feedforward control algorithm

- Monitoring strategy required to recognize changes in glucose-insulin dynamics and consequently change insulin therapy accordingly
  - Example: Physiological stress reduces *insulin sensitivity* (thus increasing insulin requirements)

Principal Component Analysis (PCA)

- PCA finds the directions of greatest variability in multivariate datasets. A dataset $\mathbf{X}$ with m rows (observations) and n columns (variables) can be expanded as

$$\mathbf{X} = \mathbf{t}_1\mathbf{p}_1^T + \mathbf{t}_2\mathbf{p}_2^T + \cdots + \mathbf{t}_k\mathbf{p}_k^T + \mathbf{E} = \mathbf{T}\mathbf{P}^T + \mathbf{E}$$

where:

$\mathbf{P} \equiv [\mathbf{p}_1\ \mathbf{p}_2 \cdots \mathbf{p}_k]$	is the matrix of n x 1 loading vectors, or PCs,
$\mathbf{T} \equiv [\mathbf{t}_1\ \mathbf{t}_2 \cdots \mathbf{t}_k]$	is the matrix of m x 1 score vectors,
$\mathbf{E}$	is the matrix of m x n residuals, and
k	is the number of PCs in the model

- The $\mathbf{p}_i$ are the eigenvectors of $\mathbf{\Sigma}$, the covariance matrix of $\mathbf{X}$:

$$\mathbf{\Sigma} = \frac{1}{m-1}\mathbf{X}^T\mathbf{X}$$

- k is chosen so that the model explains most of the variability in $\mathbf{X}$ while reducing the dimensionality of the data

Process Monitoring Based on PCA

1) PCA model is developed from a set of *training* data, $\mathbf{X}$, representative of normal conditions

2) Two statistics are calculated for each sample in the training data
   - Q statistic (a measure of model residuals)
   - T^2 statistic

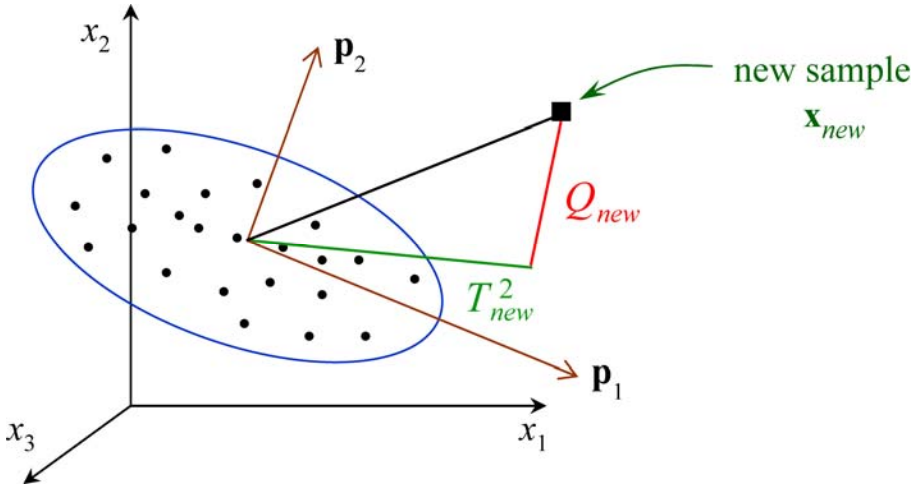
3) Confidence limits are calculated for these statistics, e.g., 95%

4) New, *test* data, $\mathbf{X}_{new}$, are projected onto the PCA model; Q and T^2 are calculated for the test data

5) Statistics for test data are compared to corresponding confidence limits; violations indicate abnormal data

Graphical Example of PCA

- Data consist of measurements of three variables: x_1, x_2, x_3
- PCA model is the $p_1 - p_2$ plane; confidence limits are represented by the ellipse
- Test data sample $\mathbf{x}_{new}$ is projected onto the PCA model
- Q and T^2 statistics for the new data sample are compared to the confidence limits



Subject Data

- The subject data collected in this research consisted of measurements of four variables:
  - **Glucose concentration, mg/dL**: Continuous (5-min) measurements
  - **Basal insulin, U/h**: Subcutaneous infusion
  - **Bolus insulin, U**: Subcutaneous infusion
  - **Meals, g CHO**: Subject-reported estimates of times and CHO content
- Two scaling methods investigated
  - Autoscaling
  - 0-to-1 scaling

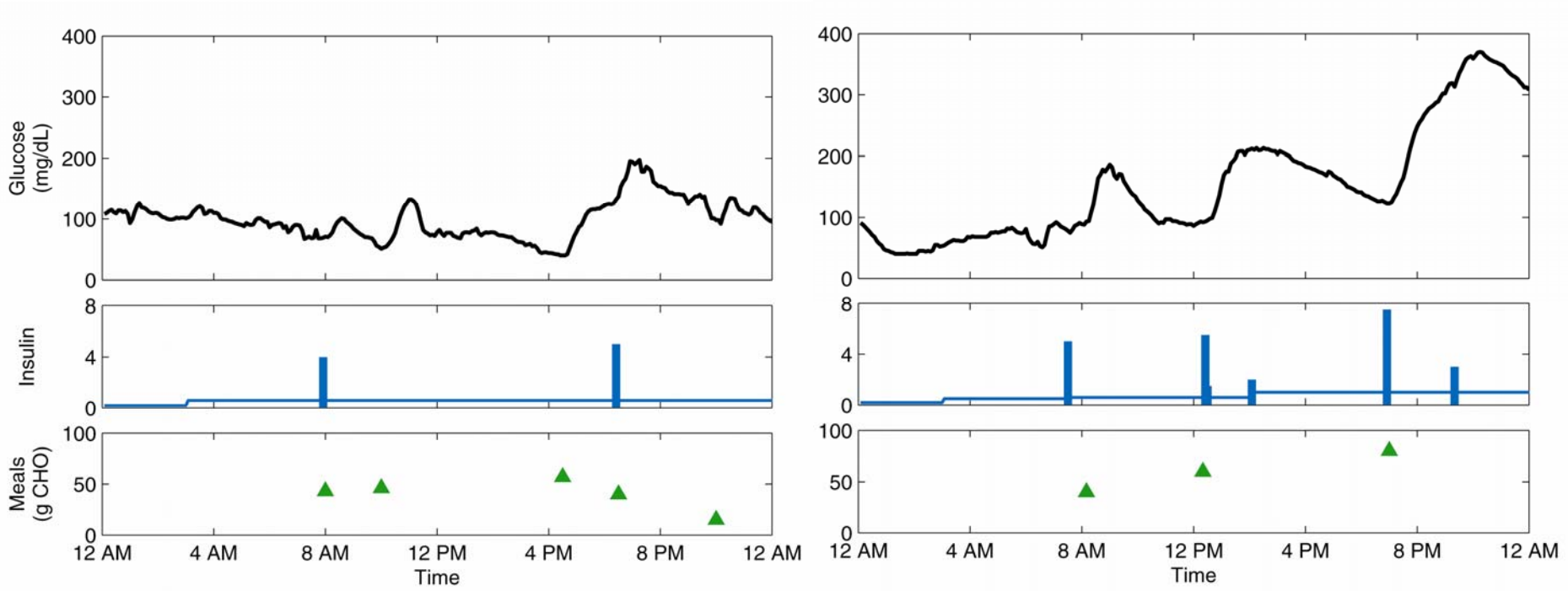
Simulated Stress States

- Initial days of data (considered normal) were collected for nine subjects in ambulatory conditions
- Six subjects were then administered prednisone, a medication that reduced insulin sensitivity (thereby simulating physiological stress), for three days
  - Some subjects' basal rates remained unchanged during the stress days
  - Some subjects' basal rates were significantly increased during the stress days to compensate for the anticipated decrease in insulin sensitivity
- Additional days of data immediately following the stress days ("post-stress" days) were collected, as well as days long after the stress days

Representative Days for One Subject

Normal Day

Stress Day



For the insulin input, the basal (continuous line) is plotted in U/h, and the boluses (bars) are plotted in U.

Monitoring Results

- False positive rate = frequency with which normal days are classified incorrectly
- False negative rate = frequency with which stress days are classified incorrectly

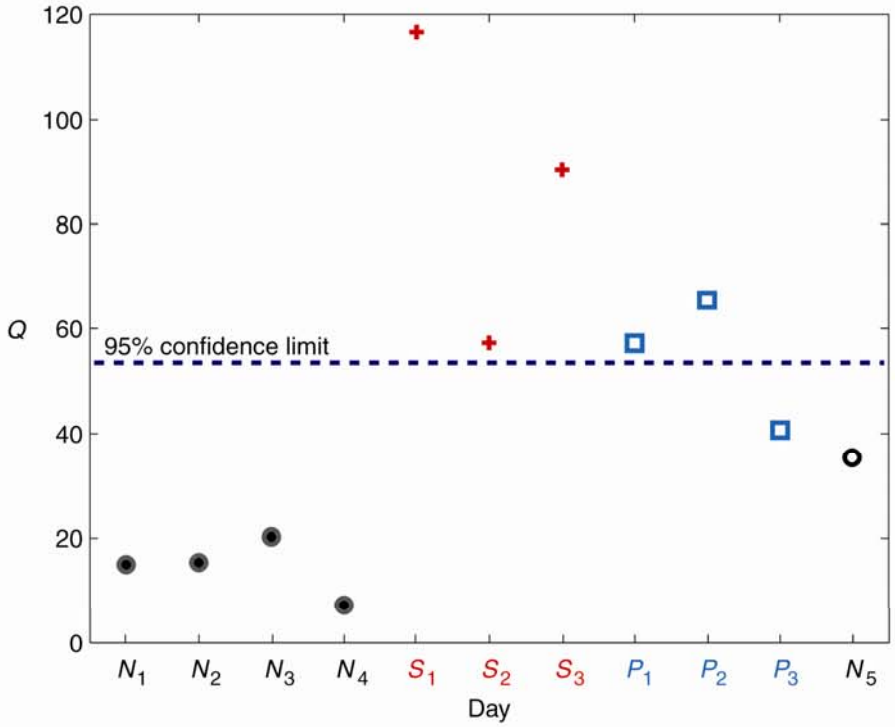
Summary of all PCA monitoring results for nine T1DM subjects.

Scaling Method	Metric	Statistic (Confidence Limit)	
		Q (95%)	T^2 (75%)
0-to-1 scaling	False positive rate	**11%**	0
	False negative rate	**11%**	56%
Autoscaling	False positive rate	53%	100%
	False negative rate	0	0

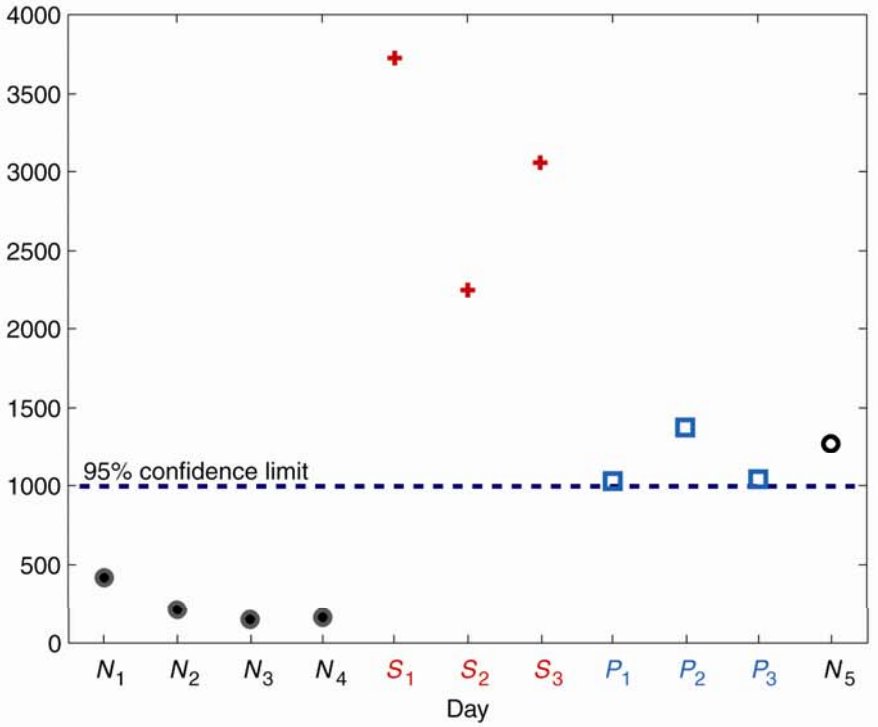
- Note: Post-stress days were not counted in the statistics due to the uncertainty of the medication's effect during these days.

Representative Results: Subject 2

0-to-1 Scaling



Autoscaling



Days N_1 – N_4: normal training days. S_1 – S_3: stress days. P_1 – P_3: post-stress days. N_5: normal test day.

Conclusions

- PCA monitoring based on clinical data from type 1 diabetes subjects can detect stress conditions
- The Q statistic is generally more sensitive than the T^2 statistic
- Best monitoring performance demonstrated false positive and false negative rates of 11% each
  - 0-to-1 scaling
  - Q statistic
  - 95% confidence limits
- Using empirically determined confidence limits may result in reduced occurrences and/or severity of misclassifications
  - Depending on whether false positives or false negatives are more severe errors, use 95% or 75% Q confidence limits, respectively

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Thank you.

PCA Scaling

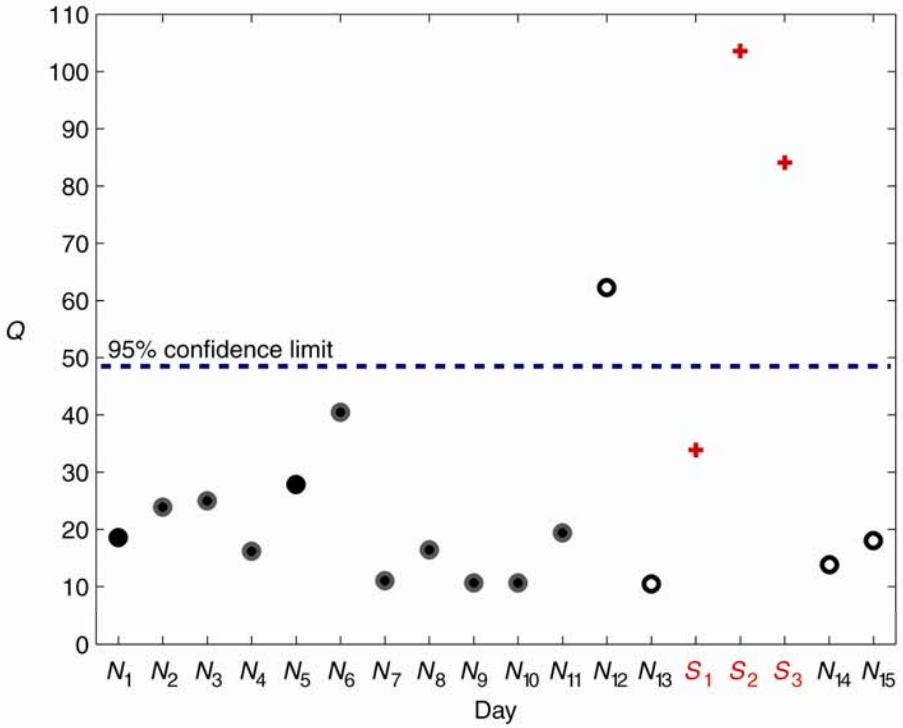
- The variables used in the PCA had different orders of magnitude:

Variable	Normal Range	Units
Glucose	40 – 400	mg/dL
Basal insulin	0.2 – 1.2	U/h
Bolus insulin	0 – 10	U
Meals	0 – 100	g CHO

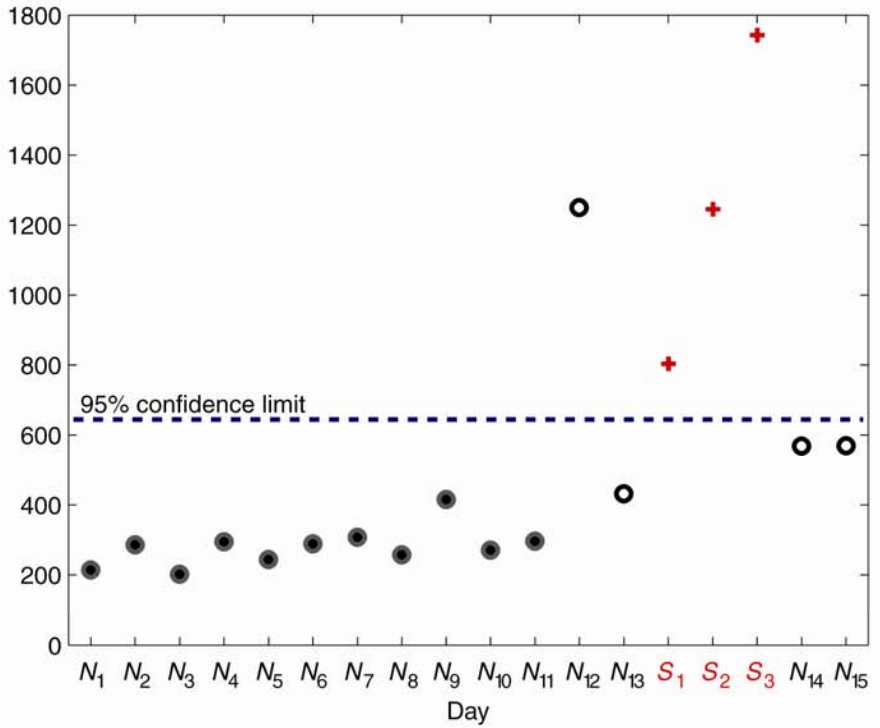
- To remove the inherent differences in the magnitudes of the variables, they were scaled two different ways
  - 0-to-1 scaling (linearly scaled to min = 0, max = 1)
  - Autoscaling (scaled to mean = 0, standard deviation = 1)
- This scaling was done on a subject-to-subject basis

Representative Results: Subject 7

0-to-1 Scaling



Autoscaling



Days $N_1 - N_{11}$: normal training days. $S_1 - S_3$: stress days. $N_{12} - N_{15}$: normal test days.

Subj. No.	Type of Day	0-to-1 Scaling		Autoscaling	
		C	I	C	I
1	Stress	3	0	3	0
	Normal	1	0	1	0
2	Stress	3	0	3	0
	Normal	1	0	0	1
3	Stress	--	--	--	--
	Normal	1	1	0	2
4	Stress	--	--	--	--
	Normal	1	0	1	0
5	Stress	2	1	3	0
	Normal	3	0	0	3
6	Stress	3	0	3	0
	Normal	2	0	1	1
7	Stress	2	1	3	0
	Normal	3	1	3	1
8	Stress	3	0	3	0
	Normal	2	0	1	1
9	Stress	--	--	--	--
	Normal	3	0	2	1
Total	**Stress**	**16**	**2**	**18**	**0**
	Normal	**17**	**2**	**9**	**10**

Subject-by-subject Results

- Results for the T1DM data using the Q statistic and a 95% confidence limit
- (C)orrect classification; (I)ncorrect classification