Feedback Regulation of Immune Response to Maximum Exercise in Gulf War Illness

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ABSTRACT

Gulf War Illness is a disease that affects about a third of the veterans that served in the 1990-91 Persian Gulf War. The symptoms are varied, the cause is unknown, and there is no known treatment. In this paper we compare the dynamic characteristics of cytokines feedback response to exercise in $n=12$ veterans diagnosed with Gulf War Illness (GWI) and $n=12$ healthy veterans deployed to the same theatre of operations. A third-order transfer function is used to model the process dynamics of 18 cytokines projected onto principal components with a Proportional Integral Derivative (PID) controller enforcing the homeostatic regulation of these co-expression patterns. Transfer functions were fit to each subject for each principal component and the dynamic response parameters compared between the veteran control and GWI subject groups. Results of this analysis indicate that while much of the regulatory response dynamics are shared by both groups, there is a significant difference in the damping of the Th1:Th2 cytokine response to exercise in Gulf War Illness.

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KEYWORDS

Exercise response; immune dynamics; feedback control; Gulf War Illness; oscillatory behavior

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1 Introduction

Gulf War Illness (GWI) is characterized as a set of nonspecific symptoms reported more frequently by veterans deployed in the Persian Gulf War (1990 to 1991) than by veterans of other conflicts. Veterans are diagnosed with GWI if they experience at least one chronic symptom from at least two of the following general categories: fatigue, mood-cognition, and musculoskeletal [1]. In 2010, approximately 250,000 of the almost 700,000 soldiers deployed during the Gulf War suffered from GWI [2]. Furthermore, a longitudinal study found that this number increased over the 10 years following their return from the war theatre [3], indicating that symptoms may have a late and gradual onset. The cause of GWI is unknown, but exposure to the organophosphate chemical warfare agents sarin and cyclosarin are suspected [4-5]. Many of the symptoms associated with GWI appear to involve altered regulation of the immune system [6].

Many alterations in immune system behavior can be observed through changes in the expression of cytokines, which are proteins that act as the chemical language of the immune system [7]. Abnormalities in cytokine trafficking have been associated with the persistence of GWI [8] and can be assessed by experimentally controlled induction of stress via a maximum exercise challenge [9-12]. In this paper we analyze the levels of 18 cytokines measured in $n=12$ GWI subjects and a control group of $n=12$ healthy sedentary Gulf War era veterans obtained from peripheral blood plasma sampled at 9 time points before during and after maximal exercise challenge. In order to identify characteristic differences in how the immune system responds to physiological challenge, the parameters of a feedback control transfer function were fit to these experimental time course data for each individual and parameter values compared across subject groups. Results of this comparison indicate that while subjects in both groups share much of the same immune response dynamics, subjects in the GWI group typically display a more sluggish co-regulation of inflammatory cytokines relative to their anti-inflammatory counterparts.

2 Methods

2.1 Experimental Data

Subjects participating in this study were all male veterans, 40 to 59 years of age, that served in Operation Desert Storm. Control and illness groups were similar in demographic profile, fitness level and body mass index. Cytokine expression levels were measured in peripheral blood plasma from 24 males, 12 of which were diagnosed with GWI and 12 healthy control Gulf War era veterans. We surveyed the expression of 18 different cytokines using an ELISA-based assay in peripheral blood plasma samples collected at 9 time points (Table 1) during a graded maximal exercise challenge. In this time course the third sample was collected at maximum exertion (maxVO₂) whereupon the subject was removed from the stationary bicycle and allowed to recover.

2.2 Data Preprocessing

The cytokine levels are first z-transformed, that is centered and range adjusted to have mean, $\mu = 0$, and variance, $\sigma = 1$. Next, cytokine co-expression features are extracted from the data (both GWI subjects and controls) using Principal Component Analysis (PCA) [13] which captures cytokine interactions as weighted sums of their expression values or latent vectors that are mutually orthogonal. Importantly, these PCA features were extracted across all individuals and as such represent cytokine interaction patterns that are common to both groups. While these interaction patterns are illness agnostic in structure, we expect that they will be over or under represented in one phenotypic group versus the other and that their response dynamics will differ. Furthermore, transforming the data via PCA allows for the decomposition of response dynamics into progressively finer levels of resolution. As such the earlier features, e.g. PC 1, essentially filter out coarse similarities in the data allowing the groups to be separated on the basis of more subtle differences more readily.

Figure 1: The normalized and PCA transformed cytokine levels for all time points and all individuals (except for the outlier). In the first two PCs, there is no visible separation between control and GWI subject samples.

In a first screening, one subject from the control group was removed from further analysis as this individual's cytokine levels were significantly different from that of all others. With this outlier removed, estimation of the PCA model produced the decomposition of overall variation (in both control and patient subjects) explained by each Principal Component (PC) show in Table 2. The first two PCs explained approximately 33% of the overall variability in the data. Samples from all time steps and all individuals (except for the outlier) are shown in Figure 1, plotted in the space of the first and second co-expression features (PCs). At this level of resolution there is no clear separation in the cytokine co-expression levels in samples from control and GWI subjects. This could imply that GWI subjects may differ not in terms of absolute co-expression, but rather in terms of the temporal response of these patterns to exercise challenge. To test this hypothesis, the score or representation of each co-expression feature (PC) at each time point was fit to a closed loop transfer function in order to extract the dynamic response parameters describing immune response to challenge in each GWI and veteran control subject.

To facilitate identification of the closed loop transfer function, the data were first interpolated with the piecewise cubic Hermite method [14] according to the measurement times to produce a uniformly sampled time course. These interpolated and resampled time courses were truncated at the T2 time point. This is done because the T3 time point is 24 hours away from the initial measurement and is intended to be used as a return to the initial resting state. However, this point is not included after interpolation because this analysis is focused on the short-term response to stress, but it is included in the interpolated values to improve the accuracy of the interpolation. Finally, all cytokine PC co-expression scores were shifted vertically by the amount of the initial measurement. This is done so that the output of the system is initially at 0, and it does not change the inherent dynamics of the cytokine signal.

Lastly, an external input $u(t)$, was assembled to represent the magnitude of the exercise disturbance for each individual.

Disturbances are set to 0 at all times except for a ramp starting at T_0 up to a value of 1 at T_1 . Each of the inputs is constructed relative to the time at which the individual reached peak exercise (T_1) (see Table 1).

Table 1: Target and approximate sample collection times (irregularly spaced) at and the corresponding exercise state. Exact times for each individual are used in the analysis.

Target Time	Approx. Elapsed Time	State
T_0	0	Resting
T_0+3	10 min.	Intermediate exercise
T_1	20 min.	Peak exercise
T_1+10	30 min.	Resting
T_1+20	40 min.	Resting
T_1+30	50 min.	Resting
T_1+60	1 h. 20 min	Resting
T_2	4 h. 20 min	Resting
T_3	24 h.	Resting

2.3 Model Class Selection and Parameter Fitting

In order to adequately select a model class, there are some considerations about the nature of the data that must be accounted for. When choosing an appropriate model class for this analysis it was useful to consider some of the properties of cytokines. For example, cytokines are pleiotropic, partially redundant, and synergistic; thus, resulting in complex behavior [7, 15-16]. Accordingly, the model class must be expected to adequately account for higher-order complex response behaviors.

Accordingly, in this analysis a fourth-order underdamped transfer function was chosen as the process feedback control model for the immune system (see Equation 1). This model class was chosen because it has a small number of parameters and yet can generalize to the more complex interactions that are associated with cytokines. Note that higher order transfer functions would require more parameters and therefore more training data to adequately fit the model.

$$G(s) = \frac{K_p}{s(1 + 2\zeta T_w s + (T_w s)^2)} * \frac{(1 + T_z s)}{(1 + T_{p3} s)} \quad (1)$$

There are 5 parameters in this transfer function that are fit to the PC cytokine scores: overall gain K_p , second-order process time constant T_w , damping factor ζ , controller time constant T_{p3} , and zero time constant T_z . Bounds are placed on the parameters to help with the highly non-linear parameter fitting over a complex landscape containing multiple local optima as well as to increase the biological relevance of the models. For example, $0.1 \leq \zeta \leq 0.9$ constrains the models to be underdamped and $-5 \leq K_p \leq 5$ was determined by the minimum and maximum cytokine feature scores in all PCs. The bounds for each of the time constants (T_w , T_{p3} , and T_z) is $0 \leq T \leq 100$. The data were fit using the System Identification Toolbox in MATLAB, release 2019A (MathWorks, Natick, MA).

2.4 Validation

Model parameter values obtained for each of the healthy subjects are compared to the parameter values found for each of the GWI subjects using the non-parametric Mann-Whitney U test [17]. This rank-based test will indicate which distribution of parameters in each PC are statistically different between subject groups. Here, a null p-value < 0.05 is considered statistically significant.

Goodness of model fit is measured using the normalized root mean square error (NRMSE) (Equation 2).

$$fit = 1 - \frac{\|x - \hat{x}\|}{\|x - \bar{x}\|} \quad (2)$$

Where x is a vector of training data, $\hat{x}$ is a vector of predicted values, and $\bar{x} = \frac{1}{n} \sum_{i=0}^n x_i$ is the average of the training data x where n is the number of training data points. The fit percentages for the models in each PC are shown in Figure 3.

Table 2: Percentage overall variability in the expression of 18 cytokines explained in each PC feature. Notice the increasingly shallow decrease in variation explained from PC 4 onward.

Principal Component	Percentage Explained
1	19.0881
2	14.4606
3	9.4789
4	8.1154
5	7.0032
6	6.4987
7	5.0663
8	4.5124
9	3.7964
10	3.6109
11	3.3219
12	3.0106
13	2.7451
14	2.5750
15	2.3282
16	1.8533
17	1.4976
18	1.0373

3 Results

Null probabilities for the Mann-Whitney test comparing parameter values across groups are presented in Table 3. There are two parameters with p-values < 0.05 , namely the dampening coefficient ζ in PC 4 and the overall gain K_p in PC 9. In other words, at the resolution of PC 4, the coefficient ζ is significantly different in the control group than in the GWI subject group. Recall that the ζ controls how much the response will oscillate. Figure 4 illustrates the difference in the magnitude of oscillations between the median trajectories in PC 4 for GWI and control subjects. Notice the significant difference at this level of detail in the combined cytokine response trajectory (Figure 4) even though there was no significant difference in the magnitude of combined cytokine expression at coarser levels of resolution (PC 1 and 2 in

Figure 1). Differences in the distributions of ζ values in PC 4 between the subject groups are shown in Figure 5.

The models capture the dynamics of the PC values which are a linear combination of the original cytokine levels. In order to draw informed conclusions about the underlying biological kinetics of a PC feature, one must analyze the corresponding feature weights for each cytokine. One sample was left out and the PCA was computed on the remaining samples; this was repeated for each of the samples. The mean cytokine weights for PC 4 are shown in Figure 6 with the standard error computed using a leave-one-out cross-validation where each sample is omitted in turn and the PC weights iteratively computed on the remaining samples. Additionally, a one-sample t-test is performed on the distribution of each cytokine weight to test if the mean is statistically equivalent to 0, signifying that the cytokine has essentially no representation in the PC (red bars in Figure 6). The raw p-values were adjusted for multiple comparison using the Benjamini-Hochberg method [18] and these adjusted p-values are used in Figure 6.

Figure 3: Median percentages fit of the models as calculated by the normalized root mean square error (NRMSE). The error bars represent the 25% and 75% interquartile range. The relatively high percentage fit (70-80%) in each PC suggests that the model class selected adequately represents this data.

Finally, cytokine weights were analyzed for outliers to uncover which, if any, cytokines have a significantly greater contribution to PC 4. Weights for Interleukin (IL)-4 and IL-10 were greater than one half of the interquartile range, indicating that they may have significantly more influence in PC 4 than the other cytokines.

4 Discussion

In this paper, we attempt to capture the interaction dynamics of 18 cytokines in response to a graded maximal exercise challenge and compare these across two groups of male Gulf War era veterans: one group consisting of health sedentary veterans and a

second group consisting of veterans from Operation Desert Storm now suffering from Gulf War Illness (GWI), a complex constellation of immune, metabolic and cognitive symptoms thought to present as a result of low-level exposures to battlefield neurotoxins. Here we deconstruct and represent at increasingly finer levels of resolution the interaction dynamics linking 18 cytokines expressed in response to maximal exercise using a linear PCA model. This differs from a more conventional univariate analysis of individual cytokines in that it focuses on co-expression patterns linking multiple cytokines in the context of one another. By virtue of this aggregation across multiple cytokines we benefit from a de-noising effect. We also benefit from the ability to decompose the dynamics of the system into various levels of detail similar in some ways to a form of detrending where one removes low frequency carrier waves to focus on detailed fluctuations that would otherwise be lost.

Figure 4: The median raw scores in PC 4 for the control and GWI samples. Median raw scores appear to oscillate less in GWI than in control subjects, in this response is more heavily damped.

Table 3: Null p-values for the 5 model parameters in each of the PCs. There are two parameters where p-values are < 0.05 (in bold), namely the dampening coefficient ζ in PC 4 and the overall gain K_p in PC 9. At the resolution of PC 4, the coefficient ζ is significantly different between groups.

PC	K_p	T_w	ζ	T_{p3}	T_z
1	0.78	0.73	0.56	0.32	0.78
2	0.93	0.69	0.88	0.60	0.31
3	0.52	0.93	0.93	0.23	0.16
4	0.21	0.31	0.01	0.98	0.46
5	0.17	0.88	0.25	0.67	0.73
6	0.48	0.19	0.52	0.31	1.00
7	0.83	0.98	0.60	0.69	0.24
8	0.44	0.73	0.12	0.83	0.85
9	0.02	0.60	0.41	0.83	0.85
10	0.98	1.00	0.69	0.69	0.73
11	0.93	0.50	0.95	0.78	0.18
12	0.12	0.23	0.23	0.56	0.95

13	0.69	0.15	0.50	0.60	0.56
14	0.48	0.06	0.08	0.06	0.73
15	0.56	0.48	0.25	0.76	0.08
16	0.52	0.41	0.90	0.27	0.17
17	0.78	0.98	1.00	0.06	0.42
18	0.73	0.05	0.62	0.78	0.73

Figure 5: A box plot of the distributions of the ζ parameters in PC 4 for control and GWI subjects. The ζ values for GWI are higher than those for the control group indicating a more heavily dampened immune response dynamic in GWI. The null p-value of the Mann-Whitney U test comparing these two distributions is 0.01, indicating that the oscillatory dynamics are significantly different between groups at this level of resolution.

As the PCA component vectors are extracted from all data regardless of clinical phenotype, these features represent co-expression patterns shared by both subject groups. Differences between groups would then manifest as differences in the overall expression and response dynamics of the feature scores. The response dynamics of each individual subject at these different levels of detail were captured as parameter values in a feedback control model consisting of a third order process model and a conventional PID controller. Median fit to data of 50% (NRMSE) or better was obtained, with most models explaining 65-85% of the recorded response. Analysis of model parameters suggested that significant differences in the dampening coefficient existed between groups in a specific co-expression pattern, PC 4, that alone explained over 8% of the variability in the 18 cytokines. Examination of this co-expression pattern indicated an inordinately high contribution of changes in anti-inflammatory cytokines IL-4 and IL-10, and opposite changes in the inflammatory cytokine Tumor Necrosis Factor (TNF)- α . Not a cytokine typically associated with exercise response, IL-4 has nonetheless been shown to mediate the analgesia produced at low-intensity exercise by modulating peripheral and central neuroimmune responses in mice with neuropathic pain [19]. It is interesting to note that no significant differences in immune feedback dynamics were found in the first 3 co-expression features each capturing 19%, 14% and 10% of cytokine co-expression respectively. In other words, roughly 40% of cytokine

co-expression dynamics in 18 cytokines were essentially conserved across groups underscoring the shared physiology in this group of male subjects in a narrow age group and sharing a common military service history. These similarities notwithstanding, the groups separate quite readily when we examine the oscillatory behavior in the ratio of anti-inflammatory to inflammatory cytokine expression, in particular as they manifest in a cytokine not normally associated with exercise such as IL-4 [12] (see Figure 6).

Figure 6: The mean weights of the cytokines in PC 4. The error bars represent one standard error from the mean. Blue (red) bars have a multiple hypothesis corrected p-value < 0.01 (p-value > 0.01) from a single sided t-test, indicating that those cytokines (do not) contribute to the PC significantly. Using outlier analysis, IL-4 and IL-10 are considered to have a significantly greater contribution to PC 4 than the other cytokines.

Differences such as these are consistent with a study by Aschbacher et al. (2012) where the parameters of a dynamic model fit to diurnal changes in hormone levels in Chronic Fatigue Syndrome and Fibromyalgia identified subgroups of these diseases [20]. Finally, it is also important to remember that this analysis focused on common cytokine constructs. It is possible that new unique cytokine signaling patterns emerge as a result of this illness that support adaptive responses unique to the GWI group. Evidence of such illness-specific differences in cytokine signaling patterns have been observed and reported previously by our group [21]. Not only does this analysis provide a compelling cytokine signature for GWI, but the methodology presented here may be used to uncover other signatures of complex immune phenotypes.

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Mandatory Disclaimer:

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