

# A Machine Learning Approach to Predicting Muscle Glycogen Use During Exercise

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## Research Article

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# Abstract

**Purpose:** Here we assess the feasibility of using machine learning models to non-invasively predict muscle glycogen use during exercise.

**Methods:** Two data sets comprised of: 1. Open-source group data from 166 studies, 2. Manually compiled granular data reported at an individual level from 8 studies published subsequently from the first data set matching the same criteria. The target variable in this study was glycogen use during exercise. Modelling was conducted on the entire data set and on four separate subsets of the data corresponding to different time durations: bands One  $t \leq 20\text{min}$ , Two  $20 < t \leq 40\text{min}$ , Three  $40 < t \leq 80\text{min}$ , and Four  $t > 80\text{min}$ . A baseline Linear Regressor model was used for reference and four models were compared to the performance of the baseline: polynomial Support Vector Regressor (pSVR), Gradient Boosting Regressor (GBR), Random Forest Regressor (RFR) and Voting Regressor. Time band models were evaluated using 3-fold cross validation.

**Results:** Baseline glycogen was identified as the most important variable influencing glycogen delta in all time bands. The best performing models were pSVR in band One, Voting Regressor in band Two, GBR in band Three and Linear and Voting Regressors in band Four. The magnitude of errors made by models increased with time band, from Mean Absolute Error (MAE) of  $41 \text{ mmol}\cdot\text{kg}^{-1}$  in band One, to MAE of  $55 \text{ mmol}\cdot\text{kg}^{-1}$  in band Four.

**Conclusion:** We present novel predictive models for estimating glycogen utilization during exercise. Our analysis demonstrates the need for individual models for specific exercise durations.

## Key Points

Here we demonstrate the ability of machine learning techniques to predicting glycogen use during exercise. We further show how these predictions can be improved when specific machine learning models are applied to different exercise durations.

We identify the features of the data set which have the greatest effect on glycogen use and show how these differ depending on the duration of exercise.

Future research should look to expand the data sets available for training machine learning models through institutional and industrial collaboration, as well as begin to explore the application of glycogen use predictions to individualization of exercise and nutrition prescription.

## 1. Introduction

Skeletal muscle glycogen content has consistently been demonstrated to have a major influence on exercise capacity and performance since it was first extracted and biochemically quantified in the late 1960's (1). Early research demonstrated glycogen content was highly susceptible to manipulation by diet,

exercise, or a combination of both (2). In addition to the regulation of exercise capacity and performance, glycogen has also been identified to play a significant regulatory role as a signaling metabolite within skeletal muscle, functioning as a molecular gauge regulating several metabolic pathways responsible for adaptation to training (3). Thus, the complex interplay between exercise, nutrition and glycogen storage has significant effects on the functional capacity of muscle, both acutely within exercise sessions and chronically in relation to a training response (4). However, current methods to quantify muscle glycogen do not provide a viable option for exercise and health practitioners to strategically manipulate glycogen levels within skeletal muscle in accordance with the desired duration and intensity of exercise, aligning to the overall training goal.

Given the importance of glycogen dynamics for exercise capacity and adaptation, there remain no practical methods to assess the effect of exercise on skeletal muscle glycogen reserves. Accurate determination of skeletal muscle glycogen is typically measured on skeletal muscle biopsies, a method that is not only invasive but also time consuming and not applicable in everyday practice. Non-invasive assessment of muscle glycogen relies on expensive technology such as MRI or positron emission tomography (5). The use of ultrasound to provide a portable practical method of measuring skeletal muscle glycogen has been proposed, however currently the technology is unable to provide reliable or accurate assessments of skeletal muscle glycogen in the field or laboratory setting (6). Given these limitations in sampling methods, accuracy, and accessibility, modelling of glycogen dynamics using machine learning (ML) to create predictive capabilities has the potential to offer a scalable and practical alternative providing information on glycogen flux in response to planned exercise-nutrition interventions.

A recent meta-analysis provided normative values of muscle glycogen at rest, during exercise, and determined the influence of different physiological parameters contributing to glycogen storage and use, advancing the understanding of glycogen dynamics (7); however, this analysis had methodological limitations (7). The predicted values were inferred using a simple linear model based on group data, and did not capture potential interactions between variables, or the possibility of non-linear relationships. Given the complex interplay of physiological systems regulating muscle glycogen breakdown, the use of more advanced analytical approaches is required to provide an integrative solution for predicting changes in muscle glycogen concentrations. Indeed, the incorporation of cross-validation and ML to develop and test models capable of prediction would be required to provide predictive capabilities for any model. Therefore, the aims of this study are to explore the suitability of different non-linear and ensemble ML models for predicting muscle glycogen utilization during exercise, considering non-linear, higher-order interactions of multiple features within the data set. This research is intended to act as proof of concept demonstrating the viability of ML models to predict glycogen dynamics during exercise, enabling practitioners and researchers to further test and apply the predictive capabilities in different applied and research conditions, generating greater sets to enable further training and refinement of ML models.

## **2. Methods**

### **2.1 Data**

The data set used for this research was made up of two sub-data sets measuring glycogen levels in humans before and after exercise. The first sub-data set comprised open-source group data from 166 studies ( $n = 417$  data points) reported as group means for groups of 4 to 20 individuals (7). The second sub-data set was manually compiled from published studies matching the study design and sampling criteria used by Areta and Hopkins (7) that were not included in the first data set or had been subsequently published in the PubMed database under the search terms “Muscle Glycogen” AND “Exercise” filtered for “Humans”. Twelve studies were identified matching these criteria and corresponding authors were contacted to request granular data, i.e., data reported at an individual level. Granular data was acquired from 8 additional studies ( $n = 122$  data points).

Studies of participants of any age, sex and physical activity level were included. Studies of cycling (upright, double-legged) at fixed intensity in either continuous or intermittent fashion (with fixed rest durations) were included. The intensity of exercise had to be reported as a percentage of  $VO_{2max}$  or calculable as such. There was no exclusion criterion for the muscle group samples for biochemical analysis of muscle glycogen. All glycogen measurements were converted to  $mmol \cdot kg^{-1}$  of dry weight (dw) units. The relevant conversion factors from wet weight to dry weight, as well as from grams to millimoles, are outlined in Areta and Hopkins (7).

Variables included in the group data were: number of participants in the trial, number of female participants, mean  $VO_{2max}$  of the group, intensity and duration of exercise, whether or not the exercise was performed to fatigue, mean glycogen concentration measured at baseline (before commencing exercise) and after the specified duration of exercise. Variables in the granular data specified the individual's sex,  $VO_{2max}$ , the intensity and duration of exercise, whether or not the exercise was performed to fatigue and the individual's glycogen concentration at baseline and after exercise.

Both group and granular data include relative  $VO_{2max}$  ( $ml \cdot kg^{-1} \cdot min^{-1}$  of body mass) and intensity as a percentage of  $VO_{2max}$ . The variable duration describes time in minutes from commencement of exercise to the time at which the corresponding post muscle biopsy was taken. For group data that represents trials with multiple measurements of the same individuals at different time points, each measurement was considered as an independent data point with the same baseline glycogen measurement. None of the studies related to granular data comprised multiple post exercise glycogen measurements. The target variable in this study is referred to as "Glycogen Delta" and is defined as the absolute difference in  $mmol \cdot kg^{-1}$  dw between the glycogen concentration measured at baseline and after a specified duration of exercise.

Data points associated with a gain in glycogen (i.e., increase from baseline glycogen after exercise) as well as any data points with missing information were removed from both data sets as appropriate. As the number of data points with missing information on sex was too large ( $n = 128$ ) and the majority were male (90%), this variable was excluded from subsequent analysis. For modeling, the group and granular data sets were combined into one final data set.

## 2.2 Four Time bands

Modeling was conducted on the entire data set as well as on four separate subsets of the data. We call these subsets time bands of glycogen utilization and define them based on duration  $t$ :

Time band One:  $t \leq 20$  ( $n = 148$ ),

Time band Two:  $20 < t \leq 40$  ( $n = 89$ ),

Time band Three:  $40 < t \leq 80$  ( $n = 154$ ),

Time band Four:  $t > 80$  ( $n = 154$ )

The rationale for this division is based on background literature (8–11), which suggests that the rate of whole-body carbohydrate and skeletal muscle glycogen utilization is greater in the earlier stages of exercise, in accordance with a greater dependency on glycogen as a fuel source. As exercise duration increases, the contribution of lipids to energy production increases, while carbohydrate contribution diminishes.

## 2.3 Descriptive Statistics

Prior to modeling, descriptive statistics were obtained for both continuous and categorical variables (Table 1). Exploratory data analysis was performed, comprising analysis of distributions of all variables and bivariate analysis of all possible variable pairs.

Table 1

Data description, continuous and categorical variables for both granular and group data, dw = dry weight, n = number of data points.

		Granular data (n = 122)				Group data (n = 417)			
<i>Continuous</i>		mean	std	min	max	mean	std	min	max
VO <sub>2max</sub>	[mL·min <sup>-1</sup> ·kg <sup>-1</sup> ]	55	13	21	75	52	8	34	73
Intensity	[% VO <sub>2max</sub> ]	71	10	51	89	71	17	30	150
Duration	[minutes]	65	64	15	240	61	50	1	241
Baseline glycogen	[mmol·kg <sup>-1</sup> dw]	427	180	125	906	490	154	150	928
Glycogen Delta	[mmol·kg <sup>-1</sup> dw]	214	125	23	772	226	135	5	629
Number of participants per group*		-	-	-	-	7	2	4	20
<i>Categorical</i>		count	proportion [%]			count	proportion [%]		
Fatigue									
Yes		0	0			63	15		
No		122	100			354	85		
Gender**									
Male		111	91			3016	89		
Female		0	0			273	8		
Missing		11	9			117	3		
*only applicable to group data									
**for group data, gender counts are reported for each individual rather than group, as some groups were mixed									

## 2.4 Modeling

To assess the utility of our features in predicting Glycogen Delta, the feature importance attribute of Random Forest regressors from Python's scikit-learn (12) package was used. Predictive modeling was conducted using the entire data set, as well as the four time band data sets separately. All models were implemented and cross-validated using the scikit-learn package. Since, to the best of our knowledge, there are no studies thus far that have applied machine learning to muscle glycogen prediction to guide appropriate selection of a regressor, five different regressors were evaluated and compared in this study. The baseline model for reference was the simplest Linear Regressor. Four models were compared to the performance of the baseline model: polynomial Support Vector Regressor (pSVR), Gradient Boosting Regressor (GBR), Random Forest Regressor (RFR) and Voting Regressor. The Voting Regressor is a meta-

estimator averaging predictions of multiple base regressors and was implemented using pSVR, GBR and RFR for general models, and the Linear Regressor, pSVR and GBR for time band models, since the RFR showed poor performance (strong overfitting) for time band models. All models were implemented using their default parameters, except for the following. RFR was implemented using the Mean Absolute Error criterion and GBR was implemented using the least absolute deviation loss function. SVR was implemented using the polynomial kernel and its parameters were set as  $C = 100$  and  $\epsilon = 1$  for the general models, and  $C = 10$  and  $\epsilon = 1$  for the time band models. All models were evaluated using k-fold cross validation. For general models,  $k = 5$  was used which resulted in test sets of approximately 20% of the whole data set. Because of the lower number of data points available for time band models,  $k = 3$  was used for time band modeling. This was done to ensure the test sets contained sufficient variation such that the underlying distribution of the data was represented. Coefficient of determination ( $R^2$ ), Mean Absolute Error (MAE) and Root Mean Squared Error (RMSE) were used to evaluate performance of models. The models identified as best performing had the highest  $R^2$  and the lowest MAE and RMSE.

## 3. Results

### 3.1 Description of data set

In the combined data set, Glycogen Delta ranged from 5 to 772  $\text{mmol}\cdot\text{kg}^{-1}$  dw, with a mean of 224  $\text{mmol}\cdot\text{kg}^{-1}$  (SD = 133). Baseline glycogen ranged from 125 to 920  $\text{mmol}\cdot\text{kg}^{-1}$ , with a mean of 476  $\text{mmol}\cdot\text{kg}^{-1}$  (SD = 162). The following are reported as mean (SD). Duration of exercise was 62 (53) minutes, Intensity was 71 (15) % of  $\text{VO}_{2\text{max}}$ .  $\text{VO}_{2\text{max}}$  was 53 (9)  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , ranging from 21 to 75  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . 12% of the combined data was associated with exercise to fatigue. See Table 1 for descriptive statistics by group and granular data.

### 3.2 Combined data modeling

A Random Forest regressor fitted on the combined dataset was used to assess feature importance in predicting Glycogen Delta. The most important variable was Duration, followed in order by Baseline glycogen, Intensity,  $\text{VO}_{2\text{max}}$  and Fatigue (whether the exercise was performed to fatigue). Table 2 shows the performance of all five regressors on the combined dataset as measured by  $R^2$ , MAE and RMSE. The Voting Regressor achieved the most notable improvement over the baseline Linear Regressor. The average MAE metric over 5-fold cross validation achieved by this model was 50  $\text{mmol}\cdot\text{kg}^{-1}$ . Furthermore, the average performance of all additional models showed an improvement over that of the baseline Linear model. However, note that the standard deviation values of RMSE and MAE achieved by the models were around 5  $\text{mmol}\cdot\text{kg}^{-1}$  dw. Therefore, models that have a difference in metrics less than the standard deviation may perform similarly on future data sets.

Table 2

Metrics achieved by the chosen models, reported as (mean, standard deviation). \*RMSE = root mean squared error (in  $\text{mmol}\cdot\text{kg}^{-1}\text{ dw}$ ), \*\*MAE = mean absolute error (in  $\text{mmol}\cdot\text{kg}^{-1}\text{ dw}$ ).

Regressor	R <sup>2</sup>	RMSE*	MAE**
Linear	0.68 (0.06)	74 (6)	59 (5)
Polynomial Support Vector	0.70 (0.04)	71 (5)	56 (4)
Random Forest	0.73 (0.07)	68 (7)	52 (7)
Gradient Boosting	0.74 (0.05)	67 (5)	52 (5)
Voting	0.76 (0.04)	65 (5)	50 (5)

The Prediction Error plots in the left of Fig. 1 (plotting measured values vs predicted values with 5-fold cross-validation) show that across all models, low values of the response variable tended to get overestimated while high values were underestimated. As shown by the residual plots in right of Fig. 1 plotting predicted values vs their residuals for five splits of test and training sets, there is a pattern of overfitting of the RFR. The Voting Regressor, averaging predictions of the pSVR, GBR and RFR, seems to show the most uniform overall performance.

### 3.3 Time band modeling

A Random Forest model fitted on each of the time band datasets was used to assess feature importance. As seen in Fig. 2, Baseline glycogen was the most important variable in all time bands, most notably in Time band Four. Intensity was second in all time bands, showing the highest importance in Time band One, and the lowest importance in Time band Four.

Performance of models on time band data is reported in Table 2, with the best performing models being pSVR in Time band One, Voting Regressor in Time band Two, GBR in Time band Three and Linear and Voting Regressors in Time band Four. Diagnostic plots showed that similarly to the models on combined data, all time band models overestimated low values and underestimated high values of Glycogen Delta. In Table 2, for three out of the time bands (all except Time band Four), non-linear regressors provided an improvement in accuracy over the Linear Regressors, in all the metrics considered. The magnitude of errors made by all models increased with each time band, from the best average MAE of  $41\text{ mmol}\cdot\text{kg}^{-1}$  in Time band One, to an average MAE of  $55\text{ mmol}\cdot\text{kg}^{-1}$  in Time band Four. It seems that as the duration of exercise increases, it becomes more challenging to accurately estimate muscle glycogen utilization based on the factors considered here. Indeed, some outliers highlighted by the models suggest there are confounding factors not captured in the data that cause the models to produce large errors.

## 4. Discussion

This study demonstrates a novel application for supervised ML to predict skeletal muscle glycogen utilization during exercise, improving the predictive capability over the use of a general linear model. The best performing models provided predictions of glycogen utilization with mean errors of 41 to 55  $\text{mmol}\cdot\text{kg}^{-1}\text{ dw}$ , showing the potential of predictive ML to non-invasively quantify glycogen use during exercise. Furthermore, using our novel approach of independently modelling different time bands, we were able to identify the best performing models for each time band and thus refine the predictive capability of our models, and highlight the need to consider complex higher order interactions when building predictive capabilities. This research highlights the potential use of applying predictive ML to complex physiological systems such as skeletal muscle glycogen utilization during exercise. The research presented here is the first demonstration of how ML integration to exercise physiology and nutrition could evolve into a powerful tool for practitioners to refine planned exercise-nutrition interventions. Previous work by Areta and Hopkins (7) used a general linear model to give normative values for resting muscle glycogen and provide insight into the modifying effects of different variables on muscle glycogen during endurance exercise. We built upon this work using ML approaches to train linear, non-linear and ensemble regressors to make predictions of glycogen utilization during exercise for the first time. Unlike Areta and Hopkins (7), we employed cross-validation to assess the performance of the models on separate data sets (test sets) and evaluated the models' suitability for the task. Our findings suggest that non-linear and ensemble regressors might be more appropriate for this prediction task, as opposed to linear regressors. In addition, we demonstrated a novel finding that the relative importance of model features varies among the time bands (Fig. 2), highlighting the need to consider the importance of different variables in predicting glycogen utilization in a context that is specific to the duration of exercise.

Given the potential differences in metabolic status of skeletal muscle over time during exercise, it is interesting that the feature importance (Fig. 2) differed between the four models corresponding to the different time bands. While baseline glycogen content was consistently identified as having a strong effect on each of the four models, the contributions of intensity,  $\text{VO}_{2\text{max}}$ , duration and fatigue were variable in their importance to each time band model (Fig. 2). While it is tempting to ascribe the contributions of different features within the time bands to physiological functions, this would not be appropriate within this analysis, given the feature importance scores are dependent on the data available for training and testing. For example, the fact that the importance of  $\text{VO}_{2\text{max}}$  decreases with duration of exercise (time band Four) may be caused by the lower variance of  $\text{VO}_{2\text{max}}$  values for the participants in trials of longer duration (i.e. trials with longer duration generally have participants with higher  $\text{VO}_{2\text{max}}$  values). This could be a function of inclusion criteria from the study or natural selection requiring a higher  $\text{VO}_{2\text{max}}$  to complete the volume of work required by the study protocol.

Our decision to use four time bands to separate the analysis allowed us to identify the best performing model within each time band and thus improve the predictive power of each model. We separated the analysis because of the well characterized shifts in substrate metabolism that occur over time during exercise at fixed intensity (8–11). Indeed, given the changes in muscle temperature (13), gas diffusion

(14) and enzyme activity, as well as changing concentrations of metabolic intermediary compounds within skeletal muscle, which alter substrate utilization at fixed intensity exercise over time (15), it would seem pertinent to compartmentalize sections of time as individual components for analysis. Given the potential differences in muscle status early in exercise (e.g., within first 0 to 10min), compared to how the same muscle will be functioning significantly later in exercise (e.g., after 90min), we highlight the potential need to consider each time domain within its own functional/metabolic limits and thus the need for different modelling within each time band. For example, the MAE and RMSE of the models were greatest in time band Four (Table 3), where we modelled exercise durations greater than 80 min. Previous research has highlighted increased variability in muscle glycogen utilization with exercise durations greater than 60min (22, 23). In parallel with time band Four, the correlation between whole muscle glycogen content pre-exercise, and time to exhaustion is reduced when exercise duration is greater than 60 min. The reduced correlation between pre-exercise muscle glycogen content and exercise capacity is likely related to the specific pattern of utilization within different fiber types, and compartments of glycogen storage within skeletal muscle (24).

Table 3

Metrics achieved by the chosen machine learning algorithms on each duration time band, reported as (mean, standard deviation). \*RMSE = root mean squared error (in mmol.kg<sup>-1</sup> dw), \*\*MAE = mean absolute error (in mmol.kg<sup>-1</sup> dw).

Regime	Regressor	R <sup>2</sup>	RMSE*	MAE**
<b>One</b> t ≤ 20	Linear	0.39 (0.13)	57 (13)	46 (10)
	<i>Polynomial Support Vector</i>	<i>0.48 (0.19)</i>	<i>52 (14)</i>	<i>41 (10)</i>
	Random Forest	0.25 (0.26)	62 (14)	50 (12)
	Gradient Boosting	0.30 (0.13)	61 (14)	48 (13)
	Voting	0.47 (0.16)	53 (15)	42 (12)
<b>Two</b> 20 < t ≤ 40	Linear	0.40 (0.10)	56 (11)	47 (9)
	Polynomial Support Vector	0.42 (0.04)	55 (11)	45 (10)
	Random Forest	0.29 (0.05)	62 (14)	50 (14)
	Gradient Boosting	0.28 (0.20)	60 (10)	49 (9)
	<i>Voting</i>	<i>0.49 (0.03)</i>	<i>52 (9)</i>	<i>43 (8)</i>
<b>Three</b> 40 < t ≤ 80	Linear	0.10 (0.16)	79 (17)	63 (13)
	Polynomial Support Vector	-0.30 (0.24)	94 (15)	69 (8)
	Random Forest	0.18 (0.10)	75 (11)	58 (9)
	<i>Gradient Boosting</i>	<i>0.32 (0.07)</i>	<i>68 (10)</i>	<i>53 (8)</i>
	Voting	0.19 (0.08)	75 (14)	58 (10)
<b>Four</b> t > 80	<i>Linear</i>	<i>0.63 (0.08)</i>	<i>71 (2)</i>	<i>54 (2)</i>
	Polynomial Support Vector	0.58 (0.17)	74 (6)	57 (4)
	Random Forest	0.55 (0.05)	79 (6)	58 (7)
	Gradient Boosting	0.54 (0.05)	79 (6)	62 (5)
	<i>Voting</i>	<i>0.63 (0.09)</i>	<i>70 (2)</i>	<i>55 (3)</i>

## 4.1 Potential factors to improve model prediction

Model outliers were identified as having an error at least three standard deviations away from the mean error (i.e., z-score greater than 3 or less than -3). Inspection of outliers in each time band suggested there may be confounding factors not captured by the features of our data, resulting in unexplained variance in the amount of glycogen utilized. For example, the pSVR in time band One overestimated glycogen utilization (by 160 mmol.kg<sup>-1</sup> dw) for a data point associated with a study by Chesley et al. (16) (i.e., the

predicted value produced by the model was 3 or more standard deviations greater than the actual result seen in the study). In this study, glycogen delta was assessed during an acute exercise session before and after a 6-day training program, and the study concluded that glycogen utilization was significantly reduced during the post-training assessment. Since our models did not consider acute training exposure, the prediction associated with the pre- to post-exercise glycogen assessment before and after the 6-day training sessions resulted in a large error. Similar outliers were found in Time band Three. Data points associated with some studies in this time band showed total glycogen utilization during exercise of around  $200 \text{ mmol}\cdot\text{kg}^{-1}\text{dw}$  (17), while others had total utilization during exercise as high as  $430 \text{ mmol}\cdot\text{kg}^{-1}\text{dw}$ . Inspection of these studies shows that their interventions differed considerably, with the former (17) incorporating structured daily training (alternating between aerobic training and high-intensity interval training), versus an acute nutrition intervention (carbohydrate loading) administered by Tarnopolsky et al (18). Therefore, there is reason to suspect the model performance of time band Three occurred due to the models' lacking features related to acute and chronic training history and short-term nutritional intervention. Other outliers produced by the models were associated with studies examining the effects of hypoxia on the regulation of muscle metabolism during exercise (19, 20). In these studies, glycogen breakdown significantly increased under hypoxic conditions. Hypoxia was not a feature in our data, thus the models presented here predicted the glycogen change associated with these data points would be much lower (by  $120\text{--}140 \text{ mmol}\cdot\text{kg}^{-1}$ ). Given the altered glycogen utilization that occurs during exercise in heat (21) accounting for ambient temperature could be an additional factor useful in predicting muscle glycogen utilization. Thus it would seem pertinent to explore the addition of these features to future models in an attempt to improve the predictive capability of ML models. Further, the addition of granular data from studies undertaken in a variety of conditions would provide greater predictive power for context specific modelling, thus improving the application of modelling to aid exercise-nutrition prescription.

## 4.2 Future work

In addition to the confounding factors presented here, it is important to note that the rate of glycogen utilization among individuals under the same conditions can still vary. Participants with similar mass, stature and  $\text{VO}_{2\text{max}}$  can present with different lactate thresholds, thus creating a different metabolic environment when exercising at the same absolute and relative oxygen consumption rate, altering the substrate contributions to energy production (26). More research data defining glycogen use in a variety of populations, where lactate threshold has been defined, has the potential to train better-performing models (7). Baseline glycogen was found to be a crucial variable in the modeling process. Therefore, to apply models for glycogen utilization in a practical training context we suggest the use of normative values presented by Areta and Hopkins (7) to inform resting muscle glycogen. However there remains scope to further refine these values through continued addition of new data.

To optimize the predictive capabilities of ML models to aid exercise and nutrition prescription we suggest there is likely a consideration of exercise intensity as a function of lactate threshold, under which specific time bands can be modeled on an individual or group basis depending on the expected duration of

exercise, considering the nutritional conditions under which exercise is commenced. The development of ML models to predict skeletal muscle glycogen use during exercise provides a non-invasive, rapid, and widely available technology that can help practitioners and researchers to refine exercise-nutrition interventions. Advancing the predictive capabilities of ML models through the addition of factors influencing glycogen dynamics, represents a significant cross-disciplinary challenge. These challenges also present a significant opportunity for collaboration to develop the area of glycolytic modelling and prediction.

## 5. Conclusion

We presented the first predictive models for estimating glycogen utilization during exercise based on individual  $VO_{2max}$ , baseline glycogen, exercise duration and exercise intensity. We applied established statistical and machine learning modelling techniques to a novel prediction problem, using a contextually large data set compiled from relevant research. Our analysis shows that modelling a complex physiological system such as glycogen dynamics during exercise requires individual models for specific durations of exercise which present with unique factor importance. Future work in ML modelling should focus on multi-lab and industry collaborations to add more variables and data to improve the accuracy of glycogen utilization prediction. This work acts as proof of concept and presents the first step towards a future of machine learning models non-invasively providing glycogen predictions that can be used to guide personalized exercise-nutrition interventions.

## 6. Limitations

Although the data set used in this work is contextually large, the information it provides presents certain limitations. First, the group data, which makes up ~ 77% of the complete data set, reports group means of glycogen concentrations and  $VO_{2max}$  values. Because of this, it is difficult to draw relationships between  $VO_{2max}$  values or baseline glycogen values and glycogen utilization on an individual level. As a feature in our models,  $VO_{2max}$  showed low relative importance, which could be a consequence of the high proportion of group data. To draw better conclusions about the relationship between individual  $VO_{2max}$  values and baseline glycogen values and glycogen utilization, it seems that more individual data is needed. Second, some of the data points used are measurements on the same individuals at different time points, i.e., they are not independent of each other. Correlations between measurements on the same individuals may lead to biased predictions of glycogen utilization from the models. When we divide the prediction problem into four time bands based on duration, it should be noted that the data in the individual time bands is not necessarily representative of the whole respective duration range of the time band. In particular, the 20-to-40-minute time band (Time band Two), 87.6% of the data corresponds to either exactly 30 or exactly 40 minutes of exercise. In the 40-to-80-minute time band (Time band Three), 56.7% of the data corresponds to exactly 60 minutes of exercise. Even though this imbalance may have led to some biases in the models, these exercise durations are analogous to the way research has been carried out previously.

# Declarations

## *ETHICS APPROVAL AND CONSENT TO PARTICIPATE*

No ethical approval was required for this analysis of data.

## *CONSENT FOR PUBLICATION*

Not applicable.

## *AVAILABILITY OF DATA AND MATERIAL*

The datasets analysed during the current study are available from the corresponding author on reasonable request. Predictive models can be accessed and used here: <http://glycogen-calculator.herokuapp.com/> .

## *COMPETING INTERESTS*

DJ, DMD, RM and SI are employees of Applied Behavior Systems Ltd. DJ, DMD, CEL, XY, RM and SI shareholders of Applied Behavior Systems Ltd. JLA declares no conflict of interest.

## *FUNDING*

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## *AUTHOR CONTRIBUTIONS*

DJ, RM, XY and SI collated and analysed the data sets. DJ, XY and SI designed and built the accompanying web application. DJ, DMD, RM, XY, CEL JLA and SI drafted and reviewed the final manuscript.

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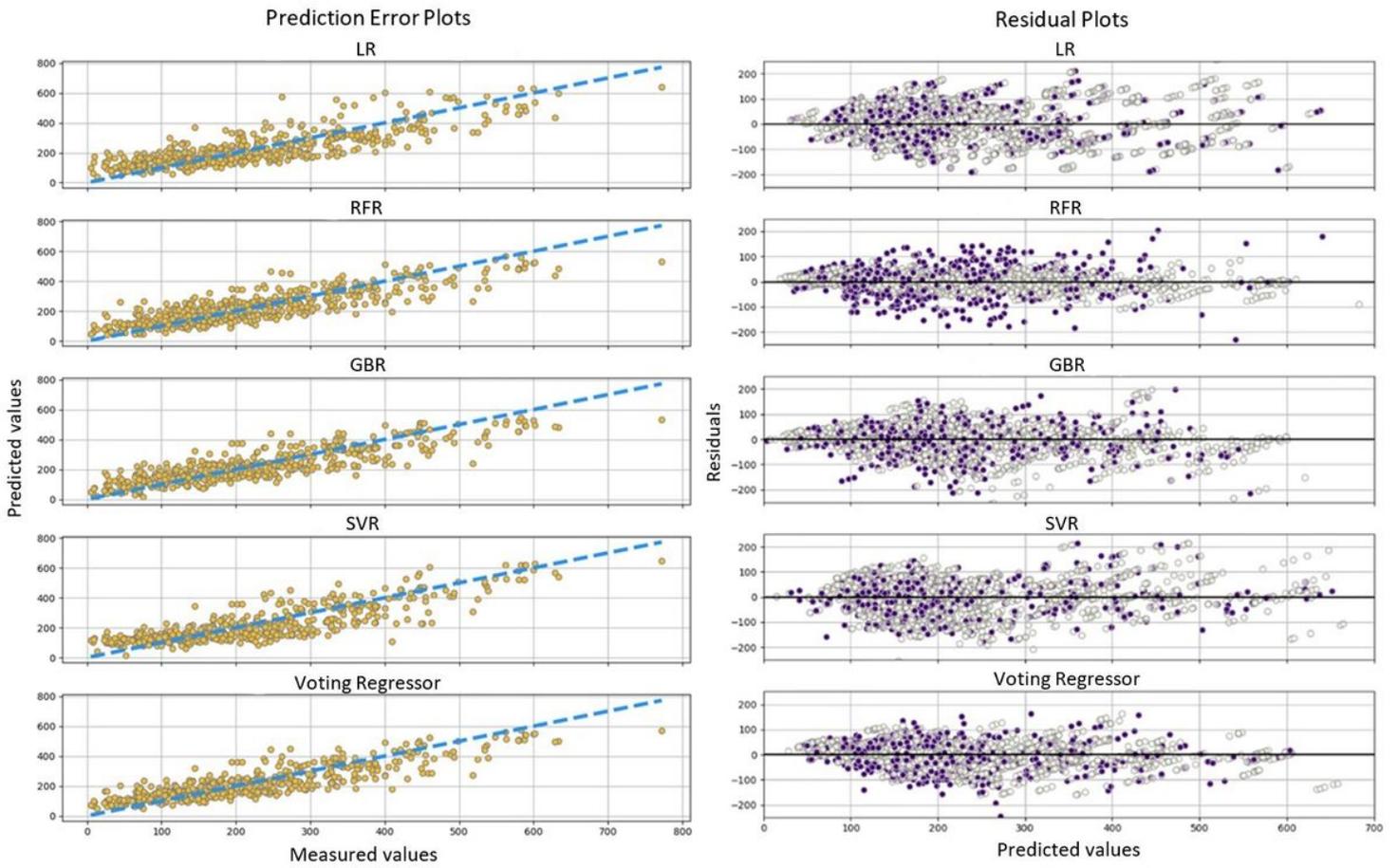
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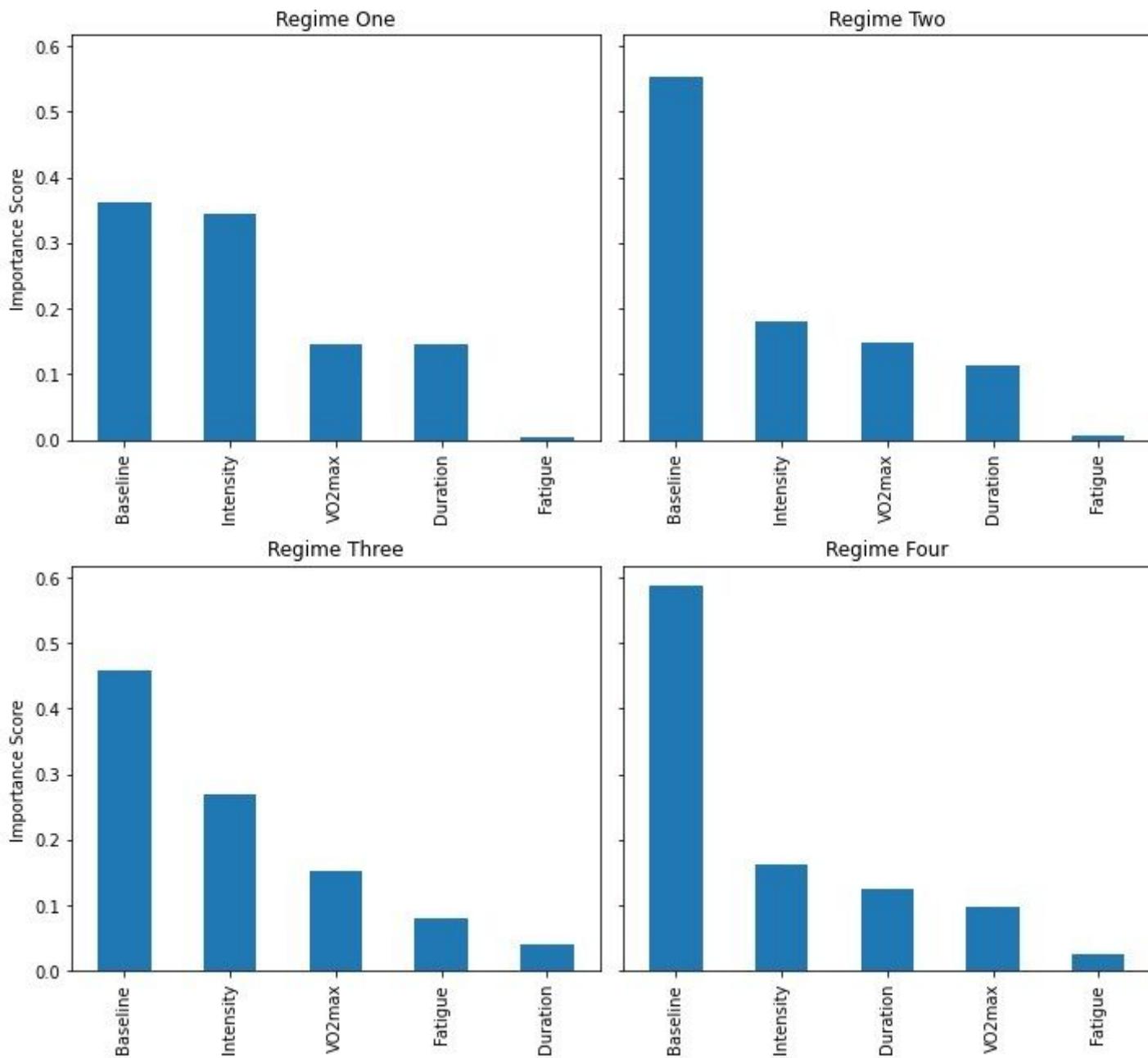
## Figures



**Figure 1**

Prediction Error plots (left) predicted versus measured values, Figure 1b: Residual plots (right) residuals versus predicted values for five splits of test and training sets.

### Feature Importances



**Figure 2**

Feature importance scores for each time band assessed by Random Forest regression.