

MODELLING OF THE CARDIOPULMONARY RESPONSES TO MAXIMAL AEROBIC EXERCISE IN PATIENTS WITH CYSTIC FIBROSIS

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28 **ABSTRACT**

29 Cystic fibrosis (CF) is a debilitating chronic condition, which requires complex and expensive
30 disease management. Exercise has now been recognised as a critical factor in improving health and
31 quality of life in patients with CF. Hence, cardiopulmonary exercise testing (CPET) is used to
32 determine aerobic fitness of young patients as part of the clinical management of CF. However, at
33 present there is a lack of conclusive evidence for one limiting system of aerobic fitness for CF
34 patients at individual patient level.

35
36 Here, we perform detailed data analysis that allows us to identify important systems-level factors that
37 affect aerobic fitness. We use patients' data and principal component analysis to confirm the
38 dependence of CPET performance on variables associated with ventilation and metabolic rates of
39 oxygen consumption. We find that the time at which participants cross the anaerobic threshold (AT)
40 is well correlated with their overall performance. Furthermore, we propose a predictive modelling
41 framework that captures the relationship between ventilatory dynamics, lung capacity and function
42 and performance in CPET within a group of children and adolescents with CF. Specifically, we show
43 that using Gaussian processes (GP) we can predict AT at the individual patient level with reasonable
44 accuracy given the small sample size of the available group of patients. We conclude by presenting
45 future perspectives for improving and extending the proposed framework.

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47 Our modelling and analysis have the potential to pave the way to designing personalised exercise
48 programmes that are tailored to specific individual needs relative to patient's treatment therapies.

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62 INTRODUCTION

63 Cystic fibrosis (CF) is the most common life shortening genetic disease in the Caucasian population,
64 affecting nearly 11,000 individuals in the United Kingdom (UK) (1). The pathology of the disease,
65 for which there is no cure, manifests itself throughout the respiratory, digestive and reproductive
66 systems of the human body. Currently, as there is no cure for CF, the management of the disease is a
67 key factor in the quality of care and health related quality of life factors. Part of the management of
68 this disease requires cardiopulmonary exercise testing (CPET) to determine aerobic fitness, as
69 represented by the maximal oxygen consumption ($\dot{V}O_{2max}$). This parameter provides a clinically
70 useful prognostic evaluation of a patient's functional capabilities. Even in mild to moderate severity
71 of CF, patients are known to demonstrate impairments in cardiac and respiratory functions leading to
72 exercise intolerance.

73

74 Enhanced aerobic fitness has been shown to improve quality of life in young patients with CF (6-18
75 years), with benefits including lower risk of hospitalisation, increased exercise tolerance, reduced
76 residual volume, increased endurance of the respiratory muscles, enhanced sputum expectoration and
77 decreased rate of decline in pulmonary function (2-6). It has also been shown from CPET that
78 individuals with CF possessing a higher $\dot{V}O_{2max}$ are shown to have a reduced mortality risk. Nixon *et*
79 *al.* (1992) reported that individuals with a $\dot{V}O_{2max}$ greater than 82% of their predicted value had an
80 83% 8-year survival rate, compared to just 28% 8-year survival rate for patients with a $\dot{V}O_{2max}$ less
81 than 58% of their predicted value (7). Furthermore, patients with a higher $\dot{V}O_{2max}$ also have
82 additional benefits in terms of improved fluid balance, retention of serum electrolytes through
83 increased plasma volume, and potential for impact on sweat gland function thus reducing thermal
84 strain and dehydration (8). These systemic changes are advantageous responses to exercise training,
85 and result in an enhanced quality of life, increased physical function and increased life expectancy (9,
86 10).

87

88 Effective management of the disease has become even more critical in recent years due to an aging
89 CF population group, with the median predicted survival of children born with CF in the UK now
90 being 45 years (1). As a consequence of an aging patient group and high medical care costs (11),
91 maintaining or enhancing fitness is crucial. Exercise has being widely acknowledged as a key
92 management strategy for CF, supported by some mechanistic data on the systemic effects of exercise
93 at the cellular level in vivo in young patients with CF (5-9). However, an integrated systems level

94 understanding of the limitations of aerobic fitness for CF patients is lacking. Measurement techniques
95 that do exist to quantify within-organ, real-time perfusion and intracellular oxygenation are invasive
96 and unethical for use with paediatric patients, and current animal model research provides limited
97 direct relevance to paediatric pathology. In clinical practice, there is significant interaction between
98 cardiac and pulmonary function and the behaviour of the systemic vasculature during exercise
99 training. This can result in the functional improvement in one part of the combined system, but
100 detrimental effects on others (9). Clinicians therefore inevitably have to adopt very imprecise
101 guidelines related to exercise prescription (12).

102

103 The use of modelling and simulation tools in clinical medicine is currently the subject of intense
104 research interest both in the UK and internationally (13-17), and the adoption of a systems
105 biomedicine approach to build and validate novel multi-scale, organ-level, integrated, re-usable and
106 re-deployable models represents a paradigm shift in biomedical modelling and simulation. There are
107 numerous organ level models in existence (18-21), however, to date there have been limited attempts
108 to either integrate these or to apply them to real clinical applications. There is ongoing basic science
109 and clinical trial work providing data on the micro (22) and macrovascular (23) changes associated
110 with exercise. These data, although important, have yet to be integrated quantitatively with other data
111 streams. In particular, there has been almost no previous work on the use of predictive modelling and
112 simulation technologies for developing treatment strategies for CF patients.

113

114 Here, we present detailed data analysis of responses to progressive exercise in patients with CF, with
115 a view of determining predictors of performance. We find that the time at which participants cross
116 the anaerobic threshold (AT), as measured by means of gas exchange threshold (GET) is well
117 correlated with overall performance. To gain further insight, we then develop a surrogate (statistical)
118 model that allows us to evaluate how CF impairs exercise tolerance relative to increasing ventilatory
119 and metabolic demands. Our modelling and analysis was based on data collected during cycling
120 exercise form a CPET at different work rates (from resting to voluntary exhaustion) in young patients
121 with CF. The outputs produced are discussed in this paper, with analyses focussing on pulmonary
122 parameters.

123

124 **METHODS**

125 Before turning our attention to modelling, we perform an exploratory analysis of the available data in
126 order to identify predictors of performance. This study was carried out in accordance with the

127 recommendations of the European Respiratory Society, written consent and assent was obtained from
128 parent(s)/guardian(s) and participants, respectively. All participants' parents gave written informed
129 consent in accordance with the Declaration of Helsinki. The protocol was approved by the South
130 West NHS Research Ethics Committee. Data were collected from 15 children and adolescents with
131 CF, who performed a valid (24) and reliable (25) combined ramp incremental and supramaximal
132 (Smax) CPET to determine $\dot{V}O_{2max}$ and the GET. This protocol was performed on an electronically
133 braked cycle ergometer, and required patients to perform an initial exhaustive ramp incremental test
134 at a pre-determined rate between 10–25 W·min⁻¹, in order to elicit exhaustion in approximately ten
135 minutes (26). After a 3-min warm-up at 10-20 W, participants completed this incremental test to the
136 point of volitional exhaustion, maintaining a cadence of 70–80 rpm throughout. Exhaustion was
137 defined as a 10 rpm drop in cadence for five consecutive seconds, despite strong verbal
138 encouragement. Active (5-min cycling at 20 W) and then passive seated recovery (10 min) then
139 preceded the Smax bout. Smax verification consisted of a 3-min warm-up (10-20 W), followed by a
140 “step” transition to a constant work rate corresponding to 110% peak power output (27). Upon
141 volitional exhaustion (defined previously), a 5-min active recovery (slow cycling at 20 W) concluded
142 the combined CPET session.

143

144 **MODEL SIMULATIONS**

145 Simulations are widely used in various fields of science and engineering because conducting physical
146 experiments is too costly, or highly time-consuming, or even impossible in some cases (28). In the
147 case of CPET in CF patients, there are also ethical considerations, since the test adds to the treatment
148 burden many children and adolescents with CF already face.

149

150 Often, a primary goal of using model simulations is to perform quantitative studies such as
151 uncertainty quantification or sensitivity analysis. Such studies are crucially important in biomedicine,
152 since there exists significant variation both between and within patient groups. Through
153 understanding and quantification of the uncertainty within the mathematical models, outcomes of
154 patient-specific interventions can be better predicted. However, such investigations require a large
155 number of runs that makes it impractical if each run takes more than a few seconds. To cope with this
156 difficulty, one can use *emulators*, also known as *surrogates*, or *metamodels* or *response surfaces*
157 (29). These provide a fast approximation of the input/output relation governed by the underlying
158 simulator. The most important classes of surrogate models have been described elsewhere (30-32).

159

160 The surrogate model employed in this study is based on Gaussian processes (GP), which have
161 become increasingly popular over the last decade (29). GPs have been used in a wide range of
162 applications from wireless communication, to obtain position estimates for a mobile user (33);
163 metallurgy, to model the development of microstructure (34); and in biology, to describe gene
164 regulatory processes and cell growth (35-37).

165

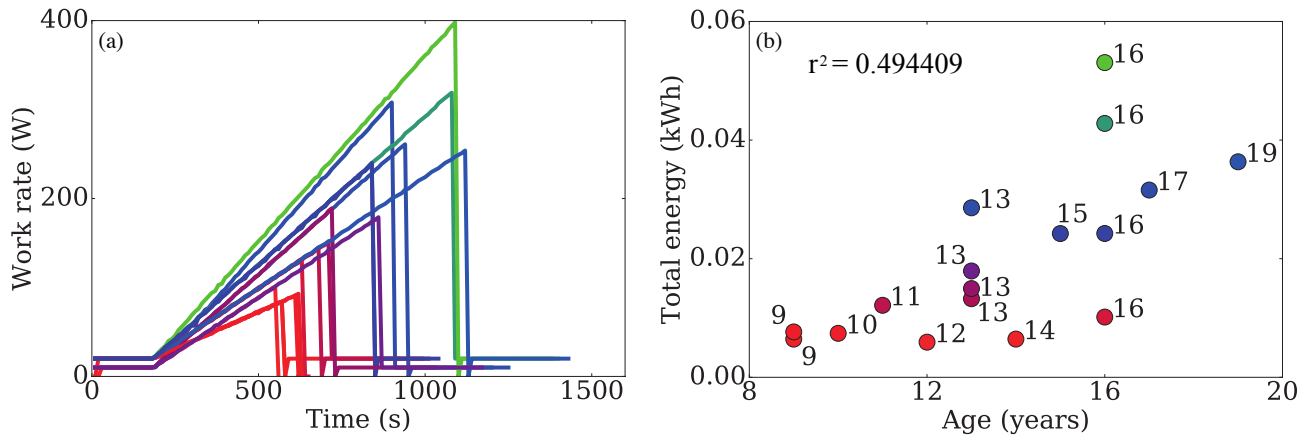
166 The data analysis was performed using Python (Anaconda Software Distribution. Version 2-2.4.0.
167 Continuum Analytics, 2016. URL <https://continuum.io>) and MATLAB and Statistics Toolbox
168 Release 2016b, The MathWorks, Inc., Natick, Massachusetts, United States. The GP model simulator
169 was implemented in R (R Core Team (2013). R: A language and environment for statistical
170 computing. R Foundation for Statistical Computing, Vienna, Austria. URL [http://www.R-](http://www.R-project.org/)
171 [project.org/.](http://www.R-project.org/))

172

173 **RESULTS**

174 *Data Analysis*

175 To facilitate understanding, we first plot in **Figure 1(a)**, raw data displaying the performance of the
176 participants. The work rate for each participant is increased at a rate that is either, a) dependent on
177 their performance in previous tests, or b) when a prior test is unavailable, at a rate that is predicted to
178 elicit exhaustion in approximately ten minutes (26). This is done in order to keep the expected
179 duration of the test comparable to other participants. Note that this means that the total energy
180 expended by a given participant is not based on the duration of the test alone. In **Figure 1(b)**, we
181 show how participant age affects overall test performance. We observe a correlation between the two:
182 the worst performing participants tend to be the youngest, but this effect is insignificant at older ages.
183 The colour coordination used in this figure (red-worst performance → blue-average performance
184 →green-best performance) will be used throughout the remainder of this section, where performance
185 is quantified by the total energy transferred during the test.

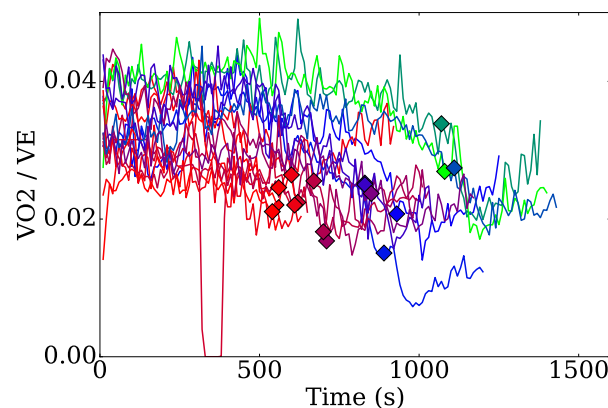


186

187 **Figure 1: (a) The work rate for each participant is increased at a rate dependent on their past**
 188 **test performance. (b) Participant age is correlated with test performance for young**
 189 **participants, but not for older ones.**

190

191 In **Figure 2**, we plot the ratio of $\dot{V}O_2$ over total ventilation ($\dot{V}E$) with respect to time. The markers on
 192 each of the time traces indicate the time of volitional exhaustion for that participant. There are two
 193 features that stand out from this figure. Firstly, participants who perform better have higher $\dot{V}O_2/\dot{V}E$
 194 ratios, suggesting that their oxygen uptake is more efficient than their poorer performing
 195 counterparts. Secondly, in the recovery phase of the test (5 minutes following volitional exhaustion)
 196 better performing participants exhibit a sharp decrease in $\dot{V}O_2/\dot{V}E$, which is not observed in the poor
 197 performance group. Again, this suggests a more efficient utilisation amongst the former group and
 198 that exhalation of CO_2 is perhaps more significant to total breathing following the test.

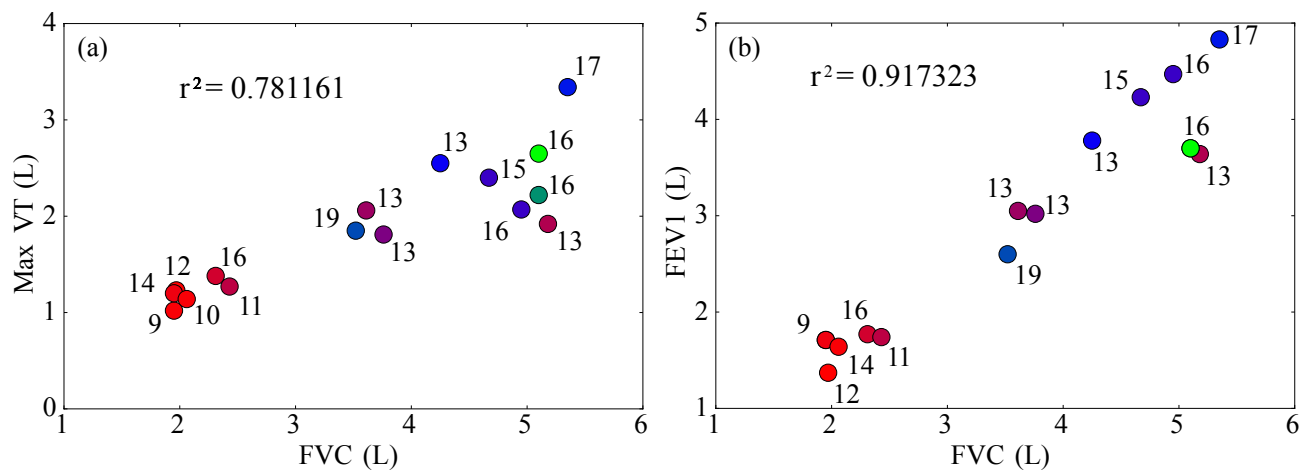


199

200 **Figure 2: Ratio of oxygen utilisation and total breathing throughout the test. Markers indicate**
 201 **the volitional exhaustion times for each participant.**

202

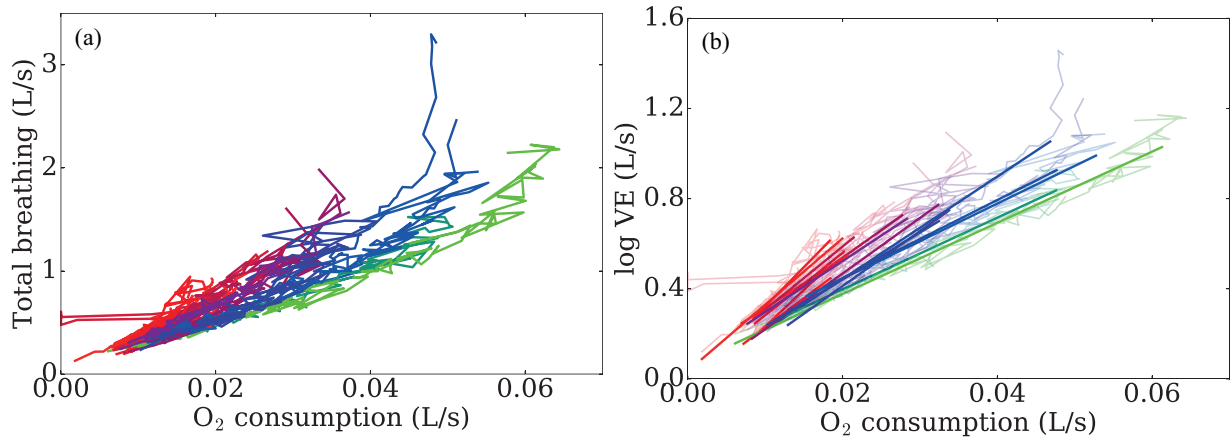
203 We next examine the effect that breathing patterns have on participant performance. Two classical
 204 prognostic measures used for patients with cystic fibrosis are the forced vital capacity (FVC), and the
 205 forced expiratory volume in one second (FEV₁). These measures have been shown to be well
 206 correlated with mortality and overall fitness of CF patient groups (38-40). In **Figure 3**, we
 207 demonstrate how these metrics are correlated with performance in the CPET test. In **Figure 3(a)**, we
 208 observe good correlation between FVC and the maximum tidal volume (TV) of breathing achieved
 209 throughout the test. This is unsurprising since participants are likely to be trying to maximise their
 210 breathing depth close to their exhaustion point. However, notice that, although the group with low
 211 FVC performed poorly, this measure was unable to separate other participants. **Figure 3(b)** reiterates
 212 this result and also highlights the high correlation between FEV₁ and FVC.



213
 214 **Figure 3: (a) Correlation of FEV₁ with the maximal tidal volume achieved throughout the test.**
 215 **(b) Correlation between FEV₁ and FVC is high. Note that, although FVC and FEV₁ are good**
 216 **predictors of poor test performance, they are unable to distinguish better performing**
 217 **participants.**

218
 219 In order to better classify the performance of the participants, we must instead look for other factors.
 220 In **Figure 4**, we present the total breathing rate against the oxygen consumption throughout the test.
 221 In **Figure 4(a)**, we find a strong relationship between test performance and respiratory pattern. Note
 222 that the curvature of the graphs suggests that an exponential fit, rather than a linear one, is most
 223 appropriate for these data. In order to test this, we take logarithms of the data and perform a linear
 224 regression, ignoring the first 180s of the test since participants are here in the warm up phase (work
 225 rate is not increasing) and the final 60s of the data prior to volitional exhaustion, since participants
 226 pass their respiratory compensation point, inducing hyperventilation and erratic breathing. The

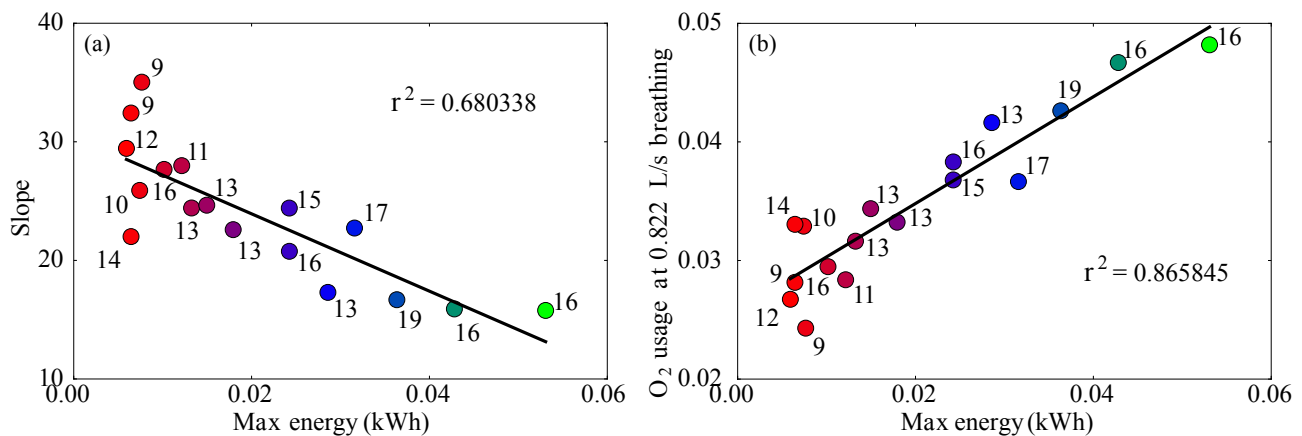
227 results of the fit are shown in **Figure 4(b)** and we can see more clearly the association of
 228 performance on breathing pattern.



229
 230 **Figure 4: (a) Total ventilation plotted against oxygen utilisation. We observe that breathing**
 231 **pattern is strongly correlated with test performance. (b) Exponential curves are fitted through**
 232 **the raw data, further highlighting this dependence.**

233
 234 From the fitted curves, we can further explore the dependence of breathing patterns on performance.
 235 Firstly, in **Figure 5(a)**, we plot the slope of the fitted curve against the total energy transfer. We find
 236 that the slope of the curve of $\log \dot{V}E$ against $\dot{V}O_2$ alone does not capture all of the variation in energy,
 237 which is highlighted by the low R-squared value (0.68). Instead, we plot in **Figure 5(b)** the oxygen
 238 consumption at a fixed rate of breathing against the total energy. Here, we find a good
 239 characterisation of the overall performance, with a much higher R-squared value (0.86), confirming
 240 that those who utilise oxygen more efficiently perform better.

241



242
 243 **Figure 5: Slope of the fitted curves ($\log \dot{V}E$ against $\dot{V}O_2$) from Fig. 4(b) plotted against the total**
 244 **energy transfer during the test. We find a relatively poor characterisation of the variance**

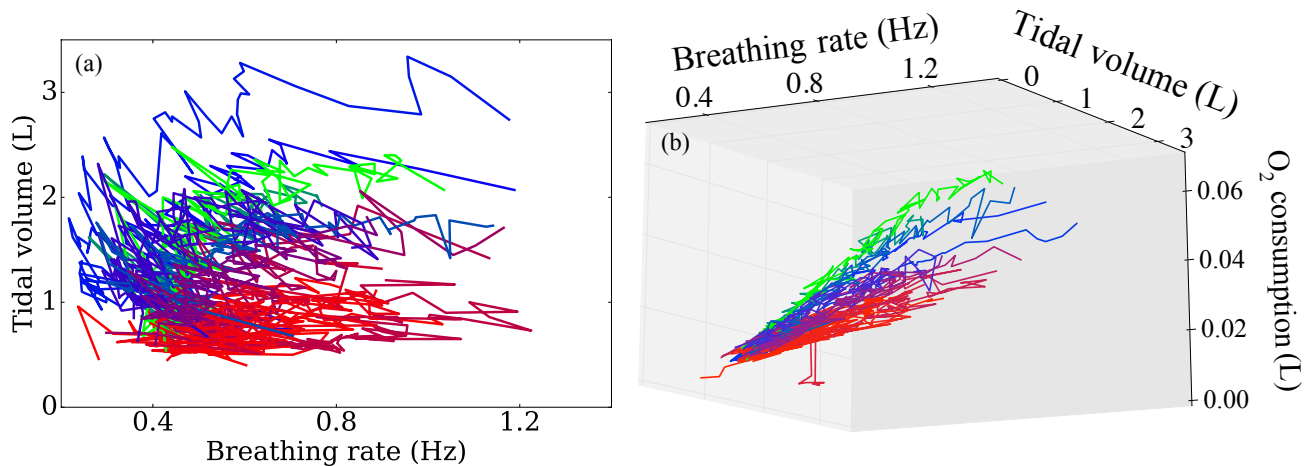
245 **between performances. (b) By instead plotting the oxygen consumption at a fixed rate of**
246 **breathing, we better capture differences in performance.**

247

248 Next, we examine the specific patterns of breathing exhibited by the participants, in particular,
249 focussing on breathing depth and frequency. Initial characterisations of these patterns seem to
250 provide little information, as indicated in **Figure 6(a)**. However, when we now also include
251 dependence of oxygen consumption, we find a near perfect classification of participants into the
252 lowest performing groups, the best performing groups and the middle group. These data are
253 displayed in **Figure 6(b)**. Note that in this figure, the trajectories appear to be evolving on a planar
254 manifold, suggesting significant co-dependence between these three variables.

255

256



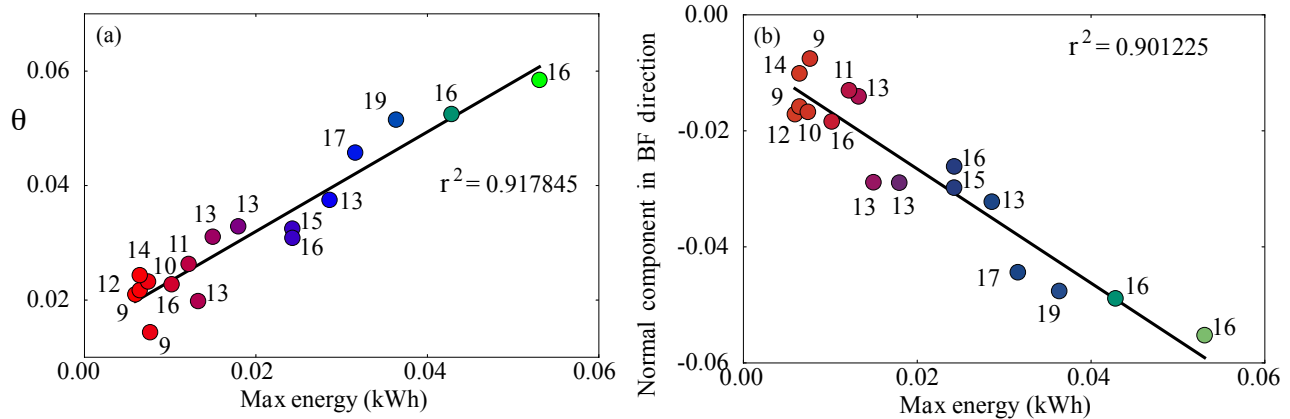
257

258 **Figure 6: (a) Breathing patterns subdivided into the breathing rate and tidal volume. These**
259 **data appear uninformative for predicting test performance. (b) With the additional inclusion of**
260 **the oxygen consumption at a fixed rate of breathing, we find that these variables now almost**
261 **perfectly capture variation in participant performance.**

262

263 Given that there appears to be co-dependence between the variables used in **Figure 6(b)**, a sensible
264 next step is to use principal component analysis (PCA) to account for these dependencies. By
265 projecting the data onto their principal components, we show in **Figure 7** how well these capture the
266 variation in participant performance. Given that there are only three independent variables in our
267 analysis, it is natural to use spherical polar coordinates to show how these quantify performance. The
268 first of these components, θ , captures over 90% of the variation in performance (**Figure 7a**), as does

269 the normal component in the direction of breathing frequency (**Figure 7b**). These results further
 270 indicate the importance of breathing frequency, together with co-variation of oxygen consumption
 271 and tidal volume as predictors of test performance.

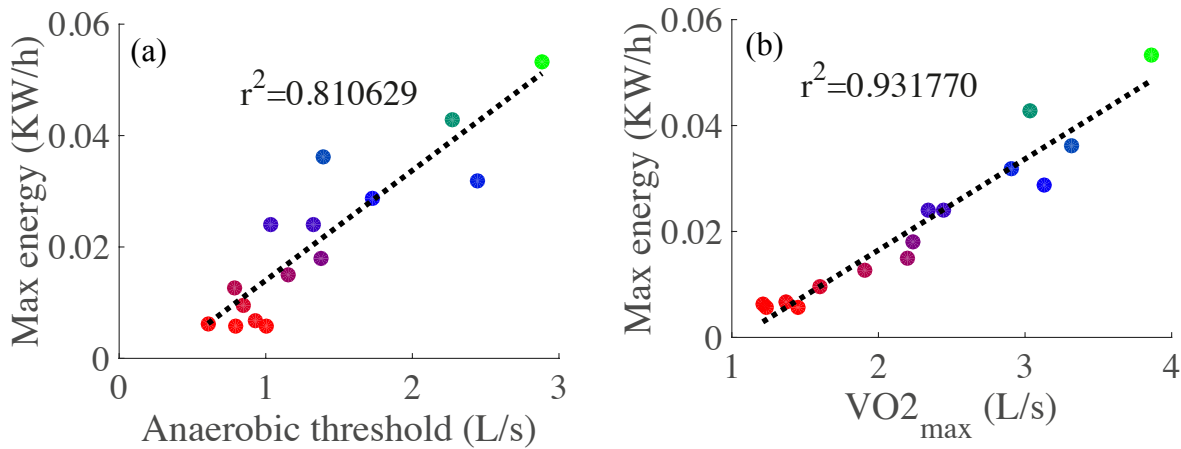


272
 273 **Figure 7: First of the principal components obtained via PCA accounts for over 90% of the**
 274 **variation in test performance. (b) Similar levels of variance are accounted for by taking only**
 275 **the normal component of the first principal component in the breathing frequency direction.**

276
 277 ***Gas Exchange Threshold***

278 Under steady state levels of exercise, the metabolic rate of production of CO_2 is assumed to be
 279 proportional to the utilisation rate of O_2 via the cellular respiratory quotient, since (after the initial
 280 rest-work transition) adenosine triphosphate (ATP) is replenished primarily via aerobic metabolism
 281 pathways. As the work rate increases, this pathway becomes unable to supply sufficient ATP to
 282 satisfy the required amount of energy and anaerobic pathways have to contribute to overcome the
 283 shortfall. In doing so, they increase the levels of waste products, such as lactate and also increase the
 284 overall production rate in CO_2 . The point at which this occurs is known as the anaerobic threshold
 285 (AT) or sometimes referred to as the lactate threshold. However, this is difficult to directly measure
 286 *in vivo* during exercise, and as such the GET is utilised as a non-invasive surrogate of the AT (41).

287
 288 The time at which participants cross the anaerobic threshold is well correlated with overall
 289 performance, as shown in **Figure 8(a)**, due to the fact that the anaerobic pathways are less efficient at
 290 producing ATP and because build-up of lactate contributes significantly to fatigue. One of the major
 291 contributing factors in defining AT is $\dot{V}\text{O}_{2\text{max}}$, since this is indicative of the limit of the rate of
 292 oxidative phosphorylation. It thus comes as little surprise that $\dot{V}\text{O}_{2\text{max}}$ is the best single predictor of
 293 CPET performance, as shown in **Figure 8(b)**.



294

295

296 **Figure 8: (a) Quantifying the relationship between the anaerobic threshold and overall test**
 297 **performance. Anaerobic thresholds were calculated using an automated procedure based on**
 298 **previous methods (41) (b) $\dot{V}O_{2\max}$ is the best single predictor of overall test performance.**

299

300 *Gaussian Processes-based Modelling*

301 A Gaussian Process (GP) defines a probability distribution over functions where the true function is
 302 considered as a particular sample path. In our modelling, we attempt to describe the influence of
 303 breathing patterns and $\dot{V}O_2$ on the AT, since this is shown to correlate well with overall test
 304 performance (see **Figure 8**). In mathematical terms, we treat AT as our scalar output variable, with
 305 input variables comprising: baseline breathing rate and tidal volumes, and O_2 consumption rates at a
 306 fixed ventilation rate, FVC, FEV₁, and the rate of changes in breathing rate and tidal at exercise
 307 onset, using the slopes calculating in **Figure 4(b)**. Thus, we have an output variable dependent on
 308 seven input variables, which we conveniently store in a vector $\mathbf{x} \in D \subset \mathbb{R}^d$, with $d=7$. We now
 309 assume that there exists a ‘true’ function $f: D \rightarrow \mathbb{R}$, such that $AT = f(\mathbf{x})$.

310

311 A GP is fully specified by its mean, μ , and covariance K , which are both functions of the input
 312 variables: $\mu = \mu(\mathbf{x})$, $K = K(\mathbf{x}, \mathbf{x}')$. Specifically, if Y is a GP, then we write:

313

$$314 \quad Y \sim GP(\mu, K): \quad \mu = E[Y(\mathbf{x})], \quad K(\mathbf{x}, \mathbf{x}') = \text{Cov}(Y(\mathbf{x}), Y(\mathbf{x}')), \quad \mathbf{x}, \mathbf{x}' \in D$$

315

316 The above can be regarded as prior distribution over function spaces. This can be seen more clearly
 317 in **Figure 9(a)**. In this subfigure, which shows a generic example of a GP, the bold red line is the
 318 ‘true’ function f . Note that the true function is unknown – our aim is to construct a model that

319 approximates it. The thin grey lines are sample paths of a GP with a zero mean prior and a constant
 320 prior covariance function. For exposition purposes, the example plot is restricted to the case $d=1$, but
 321 the approach is unchanged for $d > 1$. In principle, μ could be any function, for practical purposes,
 322 polynomial regressions are common choices. The choice of covariance function reflects our prior
 323 belief about the structure of f (such as the level of smoothness) and therefore has a crucial influence
 324 on our modelling. A typical choice for the covariance function is the squared-exponential kernel,
 325 given by:

326

$$327 \quad K(\mathbf{x}, \mathbf{x}') = \sigma^2 \prod_{i=1}^d \exp\left(-\frac{|x_i - x'_i|^2}{2\Phi_i^2}\right)$$

328

329 Here, σ controls variability of Y along the y-axis while $\Phi_i > 0, i = 1, \dots, d$, scale the distance
 330 measure for each input dimension. A more thorough exposition of common choices for the
 331 covariance function may be found in (42).

332

333 Thus far, we have defined the prior distribution for the GP. It is clear from **Figure 9(a)** that, in
 334 general, prior distributions are unlikely to provide a good approximation to the true function f . We
 335 can incorporate data (or evaluation of f at specific points), with our prior distribution to give a
 336 posterior distribution, following a Bayesian framework. The resulting posterior distribution of the
 337 GP, conditioned on the data, will be much closer to the true function.

338

339 Let $\mathbf{y} = \{f(\mathbf{x}^1), \dots, f(\mathbf{x}^n)\}$ be a set of function evaluations at n locations $\mathbf{X} = \{\mathbf{x}^1, \dots, \mathbf{x}^n\}$. Here,
 340 function evaluations correspond to the AT location for a set of patients during the CPET. Predicting
 341 with GP is obtained by conditioning Y on sample points $\Omega = \{\mathbf{X}, \mathbf{y}\}$. For any (new) $\mathbf{z} \in D$, the
 342 posterior distribution of $Y(\mathbf{z})|\Omega$ has a normal distribution with the following mean, m , and variance,
 343 s^2 :

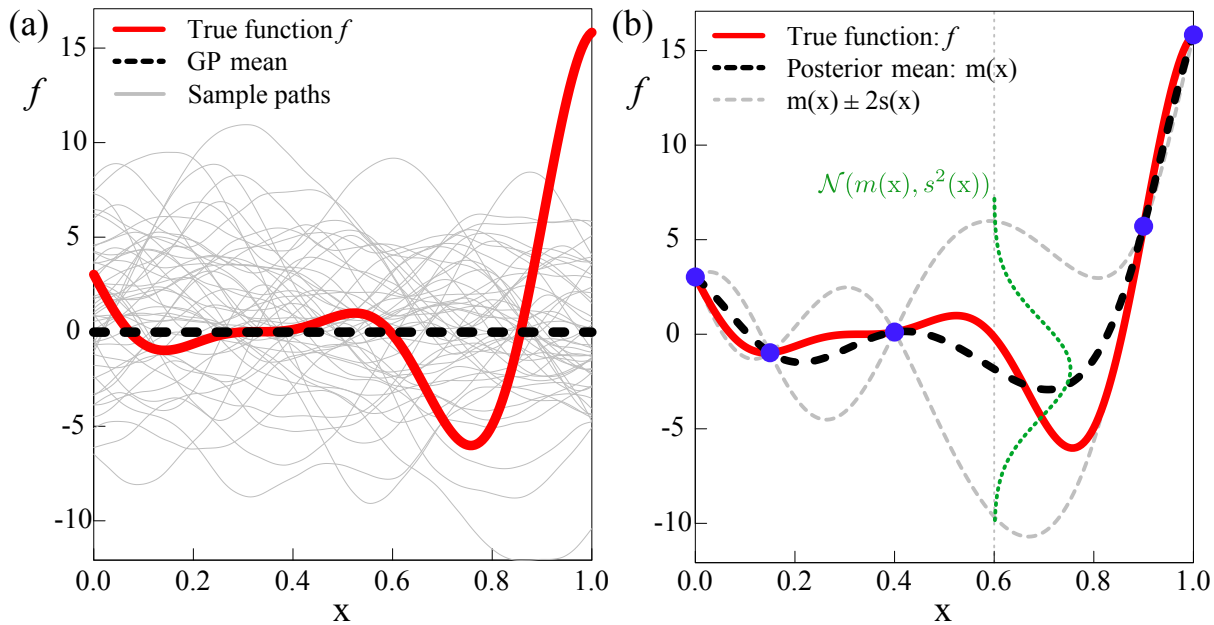
$$344 \quad m(\mathbf{z}) = \mu(\mathbf{z}) + K(\mathbf{z}, \mathbf{X})^\top K(\mathbf{X}, \mathbf{X})^{-1} (\mathbf{y} - \boldsymbol{\mu}), \quad (1)$$

$$345 \quad s^2(\mathbf{z}) = K(\mathbf{z}, \mathbf{z}) - K(\mathbf{z}, \mathbf{X})^\top K(\mathbf{X}, \mathbf{X})^{-1} K(\mathbf{z}, \mathbf{X}), \quad (2)$$

346

347 where $^\top$ denotes the transpose operator, $^{-1}$ is the inverse operator and $\boldsymbol{\mu} = \mu(\mathbf{X})$ is the vector of the
 348 mean function at \mathbf{X} . In addition, $K(\mathbf{z}, \mathbf{X})$ and $K(\mathbf{X}, \mathbf{X})$ are the covariance vector between $Y(\mathbf{X})$ and $Y(\mathbf{z})$

349 and the covariance matrix between the observations. **Figure 9(b)** shows an example of incorporating
 350 sample points to update the prior distribution shown in **Figure 9(a)**. In this generic example, the
 351 function f is evaluated at five distinct values of \mathbf{x} , and the mean and variance of the GP are updated
 352 using (1)-(2).
 353



354 **Figure 9: GP is a probability distribution on function spaces. The thick solid red line is the true**
 355 **function f and the thick dashed black line is the GP mean. (a) Thin grey lines show sample**
 356 **paths of a prior GP whose mean is zero. (b) Blue bullets indicate five data points sampled from**
 357 **f . The GP mean and covariance are updated using these sample points. The thin grey dashed**
 358 **lines show $m(x) \pm 2s(x)$.**
 359

360
 361 At the evaluated points, indicated in blue (colour online), the true value of f is known and so the
 362 variance of the GP at these points vanishes and $\mu(\mathbf{X}) = f(\mathbf{X})$. In between these points, the variance
 363 increases, dependent on the distance from an evaluated point. The mean of the GP, shown by the
 364 thick black dashed line now approximates the true function much more closely (recall that the prior
 365 mean function in **Figure 9(a)** was zero everywhere), and matches exactly at the evaluated points. The
 366 approximation can be further improved by incorporating more data (function evaluations),
 367 particularly around those input values for which the variance is high. Thus, as more data becomes
 368 available, the model is iteratively improved.

369
 370 ***Justification of Variables***

371 In our simulator, we have used the AT as our output (dependent) variable. Another choice for this
372 could be the performance in the CPET or $\dot{V}O_{2max}$, since these are the primary biomarkers for gauging
373 aerobic fitness. However, the use of the GET has been shown to have high agreement with the lactate
374 threshold (another surrogate for the AT), and related to disease severity in CF (43). Furthermore, as
375 reported in **Figure 8(a)**, the AT location for a given patient correlates well with their overall
376 performance in this test. Furthermore, by constructing a predictive model to approximate the AT
377 values for a patient, we can hope to further extend this to identify contributions of aerobic and
378 anaerobic pathways in supplying ATP to meet the demand imposed during the exercise test.

379

380 The initial exploration of results highlighted that both ventilation parameters and metabolic rates of
381 O_2 consumption were the primary factors influencing test performance. It is clear that $\dot{V}O_2$ should
382 play a significant role in determining the AT location, since it is a proxy for oxidative
383 phosphorylation which is the main pathway for ATP synthesis in steady state exercise. As a measure
384 of oxygen uptake efficiency in our model, we use the oxygen consumption rate at a fixed total
385 ventilation rate (that being 0.822 L/s) as an input (independent) variable for each patient.

386

387 There are a number of ventilatory input variables incorporated in our simulator. Given their potential
388 importance as clinical biomarkers, highlighting the limitations of lung capacity and function, we
389 include FVC and FEV_1 as input (independent) variables. During the aerobic exercise test, participants
390 spend three minutes cycling at a minimal work rate, over which we quantify their baseline breathing
391 frequency and baseline tidal volume by taking the means of these variables over this period. To
392 capture the dynamics response associated with the exercise, the rates of change of breathing
393 frequency and tidal volume are calculated, based on the fits obtained in **Figure 4(b)**. The rates of
394 change of these ventilatory variables indicate how participants respond to changes in workload and
395 were shown in **Figure 6(b)** to discriminate between participant performances. Moreover, differences
396 in rates of change of breathing frequency and tidal volume have previously been shown to be
397 significantly different between control groups and CF groups (44), suggesting that these are
398 potentially key biomarkers for assessing aerobic fitness in patients with CF.

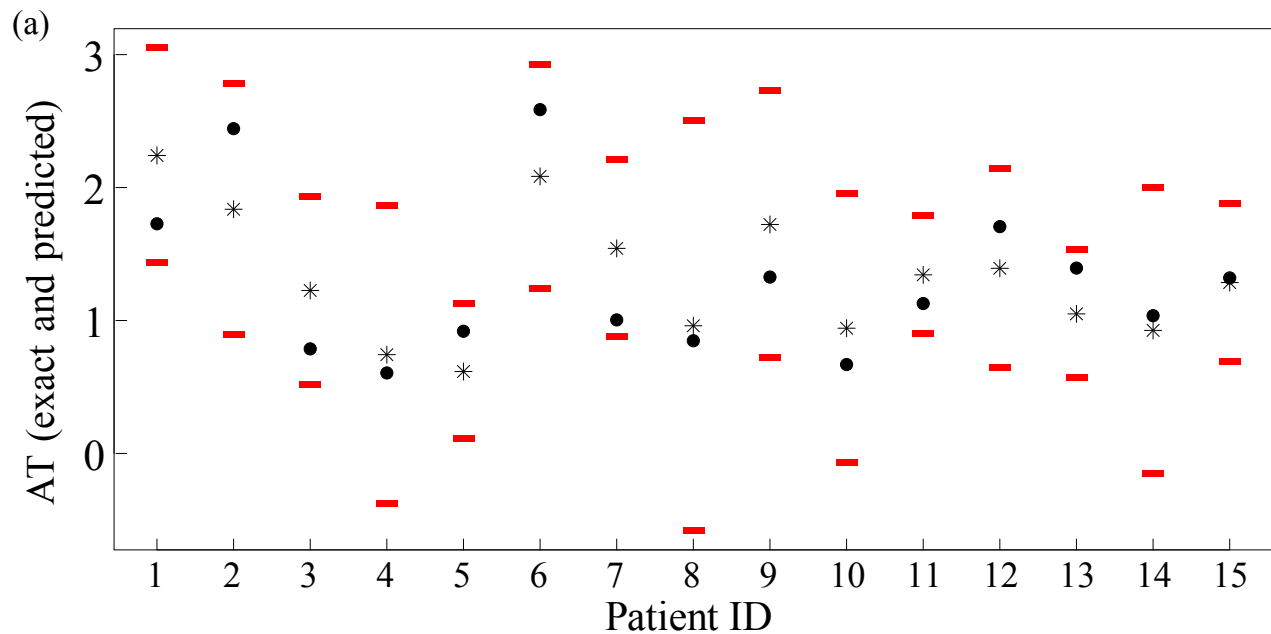
399

400 ***GP Emulator Performance***

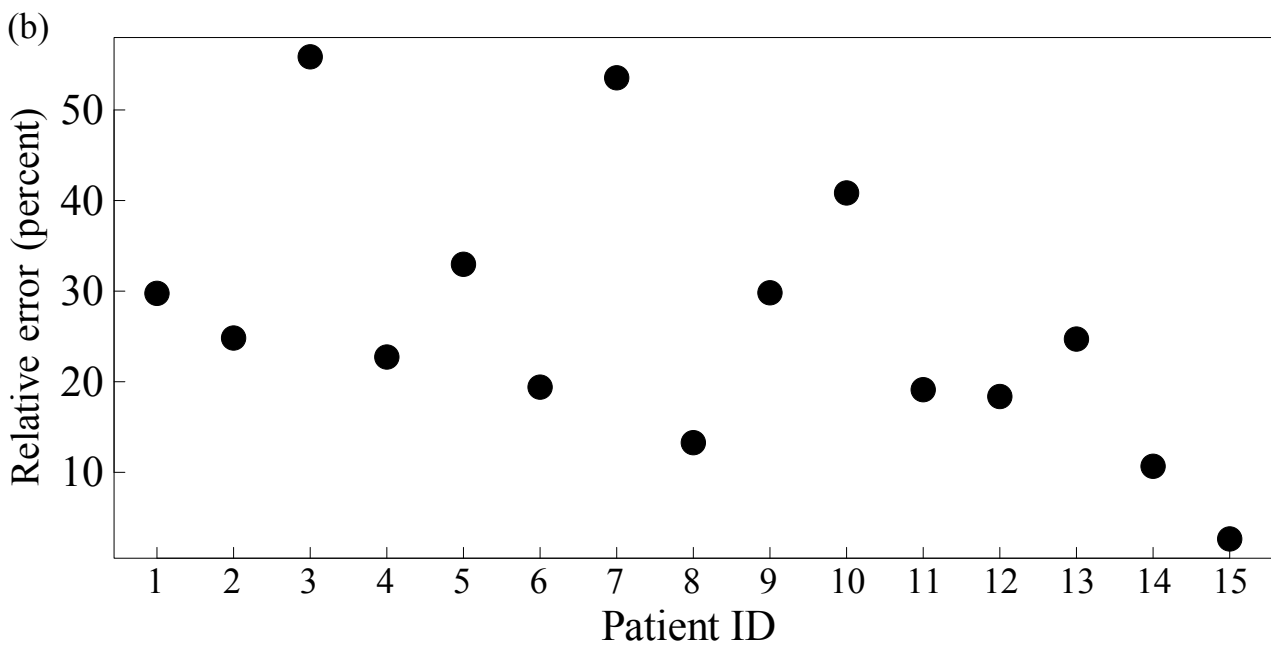
401 The GP emulator was constructed using the data presented above, with AT calculated using
402 previously described methods (41). These data were used to train the emulator. For the prior
403 distributions, a first order polynomial regression was used for the mean, whilst a squared-exponential

404 kernel with σ and Φ provided via maximum likelihood estimation was used as the prior covariance.
405 Since in this pilot study, we have a small number of participants, we use leave-one-out cross-
406 validation to assess the accuracy of our emulator, that is, for each patient, we use the emulator trained
407 against the remainder of the sample points to approximate the AT value for that patient, given their
408 input variables. The results of this are presented in **Figure 10(a)**, in which we also plot the 95%
409 confidence intervals, with relative percentage errors demonstrated in **Figure 10(b)**.

410
411



412



413

414

415

416 **Figure 10: (a) Predictions (asterisks) vs. exact values (bullets). Red bars show the 95%**
417 **confidence intervals, $m_i(x_i) \pm 1.96 s_i(x_i)$ around the predicted value, where m_i and s_i are GP**
418 **prediction mean and standard deviation based on all but the i 'th data point. (b) Relative**
419 **prediction error expressed as a percentage of the true value $f(x_i)$.**

420

421 The emulator has reasonable accuracy, in spite of the small sample size. In general, for high accuracy
422 in GP emulator, the number of sample points (corresponding to the number of patients in our case)
423 should be at least ten times larger than the number of input variables (45). Clearly, there is a need to
424 acquire further data points to improve the predictive capabilities of the emulator. For each patient, the
425 95% confidence interval around the predicted point contains the true value. Moreover, the relative
426 errors for many patients is small (considering the low sample size), though we note that some
427 patients, (3 and 7), the error is high. This highlights a need to extend this study to include more data
428 to refine estimates around these points, particularly to deal with the high variability of lung function
429 parameters in this patient group (46).

430

431 **DISCUSSION**

432 Our primary modelling aim is to eventually use the model to evaluate how CF impairs exercise
433 tolerance relative to increasing ventilatory and metabolic demands. Our predictive model could also
434 be used to evaluate therapies and their effect on exercise performance. Ultimately, we hope that this
435 will form a series of steps to design better exercise treatment that is tailored to specific individual
436 needs relative to patient's treatment therapies, a treatment modality that is affordable, and
437 personalised (47).

438

439 The data analysis and modelling results have highlighted the dependence of CPET performance on
440 variables associated with ventilation and metabolic rates of O_2 consumption. Whilst these
441 observations are, in themselves, not novel, we believe that this is the first attempt to mathematically
442 model the relationship between ventilatory dynamics, $\dot{V}O_2$ and performance in CPET within a group
443 of children and adolescents with CF. Whilst it is clear that there is much work to be done in this area,
444 we hope that this will serve as a starting point for improved modelling, not only in the arena of GP
445 emulators, but also in the domain of mechanistic modelling, which we shall describe briefly.

446

447 *Perspectives for GP improvements*

448 At present, the GP model is conditioned on specific data points for each patient. An improvement to
449 the GP could be made by instead conditioning with respect to distributions. Given that repeated tests
450 are often performed for the same individual, so that multiple sample points are provided for each
451 participant, we can consider a fit to a probability distribution capturing the variability in the identified
452 variables. This approach has advantages compared to standard GP models, such as avoiding
453 problems associated with overfitting and regularisation (which is important for the inverting ill-
454 conditioned covariance matrices that often arise during the application of (1)-(2), (48).

455

456 *Perspectives for mechanistic modelling*

457 In order to better understand and characterise the difference between performances, it would be
458 extremely useful to construct and simulate a mechanistic mathematical model, based upon on
459 ordinary differential equation (ODE) framework, describing the relationship between the
460 cardiopulmonary system and the metabolic dynamics of skeletal muscle. By describing the
461 relationships between different organ-level systems, the model would be able to identify the patient-
462 specific rate-limiting factors defining aerobic fitness. Moreover, analysis of the model could be used
463 to suggest treatment strategies to improve these factors and thus predict how patients will improve
464 under such regimes.

465

466 At the individual organ level, there are a plethora of models describing individual dynamics of the
467 level of the heart (49-52), lung (53-56) and systemic metabolic demand (57-63). There also exist a
468 number of models describing such interactions between cardiopulmonary and metabolic systems (64-
469 68) in a variety of settings, including heart failure and mechanical ventilation. A core feature in all of
470 these models is the nonlinear interaction between the constituent model compartments that
471 encompass the distinct tissues. An important consequence of this is that the model must be studied as
472 whole, in an integrated fashion, to truly understand the body's response to exercise.

473

474 With respect to the present question, there are a number of limitations of the existing modelling
475 approaches. Most significantly, none have been designed with either an adolescent, or a CF patient
476 group in mind, and the nuances of these patient groups will have to be factored into to any model
477 development. In particular, these models have relatively simple, empirical models to describe
478 changes in ventilation, which may not capture breathing dynamics of our patient group well.
479 Moreover, to the best of our knowledge, no model considers the changes in ventilation separated into

480 breathing frequency and depth that have been shown by us and others (44) to be critical to overall test
481 performance.

482

483 In our analysis, we have demonstrated that the AT or GET location is a critical factor in determining
484 overall patient aerobic fitness. Many of the mathematical exercise models describe only steady-state
485 exercise, in which aerobic pathways meet most of the ATP demand (64-68). As such, these models
486 are inadequate to capture the dynamics we describe here. Another common topic of study is the
487 dynamic response at exercise onset, which again, does not meet the current need to describe the AT
488 crossing point (69-72).

489

490 Of the mathematical models that describe the contribution of anaerobic pathways to ATP production,
491 some assume that the shortfall in meeting ATP demand via oxidative phosphorylation is met entirely
492 by anaerobic pathways (73), yet this is clearly not so, since ATP levels in skeletal muscle post-
493 exercise may be up to 30% lower than pre-exercise values (74). Mathematical models that factor in
494 fatigue brought about by anaerobic metabolism are generally phenomenological in nature, and it is
495 difficult to quantify these models against real patient data (73, 75, 76), and these models mostly fall
496 outside the arena of ODE-based modelling and so dynamical properties are difficult to infer from
497 them.

498

499 Developing a mathematical model to describe the integrated behaviour of all of the relevant organs,
500 whilst remaining biophysically plausible, but without requiring excessive or invasive
501 parameterisation is a difficult task. The proposed model should include descriptions of the
502 cardiovascular system, the ventilatory system and simple models of metabolism at the tissue level.
503 Specifically, dynamic variables should include alveolar, arterial, venous and tissue level partial
504 pressures/concentrations of O_2 and CO_2 , cardiac output, ventilation and metabolic rates oxygen
505 utilisation and CO_2 production. Partial alveolar gas pressures can be linked to data collected during
506 the test, and the work rate can then be provided as inputs to the model. Note that these variables are
507 similar to those included in previously defined models (64-68) and the aim is to extend these to
508 describe the dynamics observed in patients with CF. The proposed model schematic is displayed in
509 **Figure 11.**

510

511 Of critical importance to the overall model construction is the development of a simple, yet realistic
512 model of cellular metabolism, to overcome the issues discussed earlier. The model should respect the

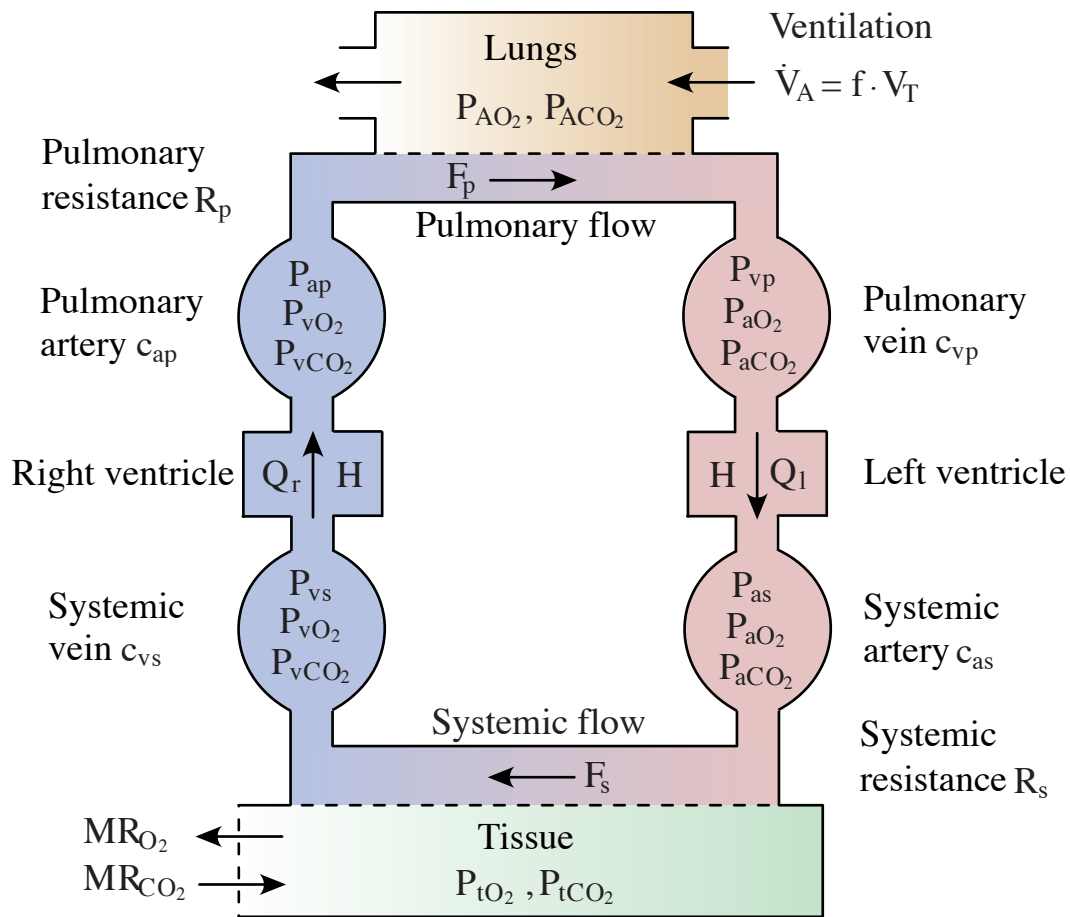
513 different metabolic processes that occur in the muscle tissue, in particular: glycolysis,
514 phosphocreatine breakdown and synthesis and oxidative phosphorylation, in a simplistic fashion that
515 is amenable to being fit to CPET data. Whilst there are models that describe the biochemical
516 reactions associated with these processes, and importantly, their stoichiometry (58, 61, 63, 67, 77),
517 quantifying their associated rate constants *in vivo* is a near-impossible task, and so efforts must be
518 made to develop a model that incorporates the relevant metabolic dynamics whilst being simple
519 enough to be fit to data.

520

521 With knowledge of the integrated system, attempts can also be made to describe other important
522 exercise-based processes, such as lactate buffering and recycling (as a fuel source) (61, 78, 79) and
523 the overall muscle fatigue brought about by the combination of all of these factors. Only by
524 systematically exploring the dependence of aerobic fitness of all of the factors described in this
525 section can we begin to understand the system in an integrated fashion.

526

527



528

529

530 **Figure 11: Schematic of the variables and processes in the proposed ODE-based mathematical**
 531 **model. Adapted from Timischl (1998) (66) and Batzel *et al.* (2005) (80).**

532

533 **LIMITATIONS**

534 A limitation with the current study is the utilisation of a relatively small sample size, and this may be
 535 contributing towards aforementioned errors. Future studies should seek to utilise CPET collected
 536 annually in CF centres, to develop larger, multi-centre, samples whereby a uniform exercise protocol
 537 is utilised. Given that utilisation of CPET is now recommended and endorsed for regular use by
 538 international medical societies (81), and individual CF centres are reporting upon experiences of
 539 using CPET (82), large-scale utilisation of such data is a feasible target.

540

541 The findings presented may be derived from a smaller sample, and therefore the models presented are
 542 only preliminary results for this patient cohort; however, the study provides a unique examination
 543 into the aerobic and anaerobic signatures of individual patients with CF in response to progressive
 544 exercise.

545

546 Finally, whilst this study provides an insight into metabolic process during exercise, future research
547 and models must account for additional variables predictive of function and mortality (e.g. genotype,
548 body composition, pancreatic sufficiency, infection status, exacerbations (83, 84)) and co-morbidities
549 (CF-related diabetes (85), pulmonary arterial hypertension (86)) existent within CF, notably those
550 that may affect exercise tolerance.

551

552 **CONCLUSIONS**

553 Benefits of modelling include the ability to utilise existing data sets at a time when there are limited
554 resources. There is also a call to reduce the burden on sick patients (EU directive). As models
555 improve and the quality of fits to data are improved, the models can be used in a prognostic setting to
556 predict potential improvements in aerobic fitness that may arise due to therapeutic intervention.
557 Moreover, with proper mechanistic modelling of the primary organs affected in CF, there exists the
558 potential to optimise treatment for this patient group by identifying the limiting factors of aerobic
559 fitness.

560

561 **CONFLICT OF INTEREST**

562 *The authors declare that the research was conducted in the absence of any commercial or financial*
563 *relationships that could be construed as a potential conflict of interest.*

564

565 **AUTHOR CONTRIBUTIONS**

566 CAW conception, design of the work, data collection, analysis, interpretation, manuscript drafting,
567 final approval of the version to be published, agreement to be accountable for all aspects of the work
568 in ensuring questions related to the accuracy and integrity of any part of the work are appropriately
569 investigated and resolved; KTA data interpretation, critical review of the paper, final approval of the
570 version to be published, agreement to be accountable for all aspects of the work in ensuring questions
571 related to the accuracy and integrity of any part of the work are appropriately investigated and
572 resolve; OWT data collection, analysis, interpretation, final approval of the version to be published,
573 agreement to be accountable for all aspects of the work in ensuring questions related to the accuracy
574 and integrity of any part of the work are appropriately investigated and resolved; KW supervision of
575 work organization and development, data analysis, interpretation, manuscript drafting, final approval
576 of the version to be published, agreement to be accountable for all aspects of the work in ensuring
577 questions related to the accuracy and integrity of any part of the work are appropriately investigated

578 and resolved. HM construction of GP emulator, final approval of the version to be published,
579 agreement to be accountable for all aspects of the work in ensuring questions related to the accuracy
580 and integrity of any part of the work are appropriately investigate and resolved.

581

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584

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590

591 **Supplementary Material**

592 Supplementary Material should be uploaded separately on submission, if there are Supplementary
593 Figures, please include the caption in the same file as the figure. Supplementary Material templates
594 can be found in the Frontiers Word Templates file.

595 Please see the [Supplementary Material section of the Author guidelines](#) for details on the different
596 file types accepted.

597

598

599

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810 **Figure Titles**

811 **Figure 1: (a) The work rate for each participant is increased at a rate dependent on their past**
812 **test performance. (b) Participant age is correlated with test performance for young**
813 **participants, but not for older ones.**

814

815 **Figure 2: Ratio of oxygen utilisation and total breathing throughout the test. Markers indicate**
816 **the volitional exhaustion times for each participant.**

817

818 **Figure 3: (a) Correlation of FEV₁ with the maximal tidal volume achieved throughout the test.**
819 **(b) Correlation between FEV₁ and FVC is high. Note that, although FVC and FEV₁ are good**
820 **predictors of poor test performance, they are unable to distinguish better performing**
821 **participants.**

822

823 **Figure 4: (a) Total ventilation plotted against oxygen utilisation. We observe that breathing**
824 **pattern is strongly correlated with test performance. (b) Exponential curves are fitted through**
825 **the raw data, further highlighting this dependence.**

826

827 **Figure 5: Slope of the fitted curves ($\log \dot{V}E$ against $\dot{V}O_2$) from Fig. 4(b) plotted against the total**
828 **energy transfer during the test. We find a relatively poor characterisation of the variance**
829 **between performances. (b) By instead plotting the oxygen consumption at a fixed rate of**
830 **breathing, we better capture differences in performance.**

831

832 **Figure 6: (a) Breathing patterns subdivided into the breathing rate and tidal volume. These**
833 **data appear uninformative for predicting test performance. (b) With the additional inclusion of**
834 **the oxygen consumption at a fixed rate of breathing, we find that these variables now almost**
835 **perfectly capture variation in participant performance.**

836

837 **Figure 7: First of the principal components obtained via PCA accounts for over 90% of the**
838 **variation in test performance. (b) Similar levels of variance are accounted for by taking only**
839 **the normal component of the first principal component in the breathing frequency direction.**

840

841 **Figure 8: (a) Quantifying the relationship between the anaerobic threshold and overall test**
842 **performance. Anaerobic thresholds were calculated using an automated procedure based on**
843 **previous methods (41) (b) $\dot{V}O_{2\max}$ is the best single predictor of overall test performance.**

844

845 **Figure 9: GP is a probability distribution on function spaces. The thick solid red line is the true**
846 **function f and the thick dashed black line is the GP mean. (a) Thin grey lines show sample**
847 **paths of a prior GP whose mean is zero. (b) Blue bullets indicate five data points sampled from**
848 **f . The GP mean and covariance are updated using these sample points. The thin grey dashed**
849 **lines show $m(x) \pm 2s(x)$.**

850

851 **Figure 10: (a) Predictions (asterisks) vs. exact values (bullets). Red bars show the 95%**
852 **confidence intervals, $m_i(x_i) \pm 1.96 s_i(x_i)$ around the predicted value, where m_i and s_i are GP**
853 **prediction mean and standard deviation based on all but the i 'th data point. (b) Relative**
854 **prediction error expressed as a percentage of the true value $f(x_i)$.**

855

856 **Figure 11: Schematic of the variables and processes in the proposed ODE-based mathematical**
857 **model. Adapted from Timischl (1998) (66) and Batzel *et al.* (2005) (80).**

858