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State dependence: Does a prior injury predict a future injury?

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ABSTRACT

The sports medicine literature is filled with associations between injury and causal factors. However, those results have been inconsistent. We're left wondering which of our athletes might need more attention and where our efforts might be best spent. Resistance to injury is the result of interaction between many variables. These variables are interdependent with dynamic relationships which can be sometimes correlated, at times anti-correlated and from time to time show no relationship with injury risk. Relationships we may have seen yesterday do not necessarily hold true for today and we should not use those to infer what will happen. This perspective piece builds on prior works and describes how the complex interaction between injury determinants presents in other systems, why determinants are not stable and instead vary over time due to internal and external forcing and why our prediction ability remains limited even when determinants are identified. Patterns built from frequent time series data in conjunction with nonlinear dynamical methods can offer us a new approach to thinking about injury prediction.

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1. Introduction

Exercise science and sports medicine professionals have developed models in order to predict which athletes are at greater risk of injury (Grygorowicz et al., 2017; Hewett et al., 2005; Khayambashi, Ghoddosi, Straub, & Powers, 2016). But, the association between factors which may affect injury risk and the relative contribution of individual factors to subsequent injury risk have not been consistent and we are left wondering which athletes might need more attention and where our efforts might best be spent (Grimm, Jacobs, Kim, Denney, & Shea, 2015; Taylor et al., 2018; van Dyk et al., 2016, 2017). Explaining the variation in relationships among the factors thought to predict injury and the inability of these factors to consistently demonstrate predictive value remains an unmet goal. Some of these relationships will be uncovered as researchers and sports medicine professionals increasingly collect frequent time series observations of athletes using GPS, heart rate monitors and other devices (Stern, Hegedus, & Lai, 2020). Perhaps by further examining context-dependent relationships using a nonlinear dynamical systems approach, we may develop new

methods to understand these complex relationships. The utility of this approach has been demonstrated by applying these tools to chronic diseases, electrical power systems, quantum physics, physiology, neurobiology and other fields (Cai, Lai, & Winslow, 1993; Rikkert & Dakos, 2016; Dhamala & Lai, 1999; Doiron, Litwin-Kumar, Rosenbaum, Ocker, & Josic, 2016; Han, Xu, & Lai, 2020; Sugihara, Allan, Sobel, & Allan, 1996; Ye & Sugihara, 2016).

1.1. Can eating a grapefruit kill you?

Suppose a patient you are seeing begins taking a drug, Simvastatin, to help control their cholesterol and soon afterward this patient develops rhabdomyolysis and kidney failure. Although we may identify a strong relationship between taking Simvastatin and these complications, should we predict that Simvastatin is the cause and that the patient will do better with a lower dose or a different medication? Consider that this same patient eats a grapefruit daily. Eating grapefruit impairs the body's ability to metabolize over 85 different commonly prescribed drugs resulting in dramatically increased bioavailability (Bailey, Dresser, & Arnold, 2013). Viewing a snapshot of the patient's health each day over a period of time we might see a positive relationship between the patient's health and simvastatin for some time as their cholesterol levels improve and then a negative one as the patient begins eating

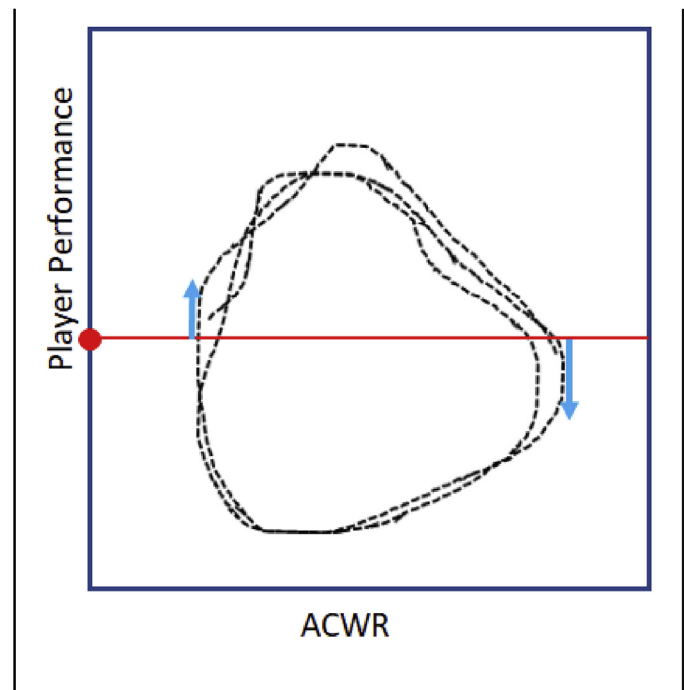
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grapefruit (See Box 1). The estimated incidence of rhabdomyolysis in individuals taking a statin with concurrent consumption of grapefruit juice is 5–6 per 100,000 person year (Lee, Morris, & Wald, 2016). Death of muscle cells and the release of their constituents into circulation may be referred to as the *cause* of rhabdomyolysis while other factors involved in the development of rhabdomyolysis may be referred to as *sufficient causes* (Rothman, 1976). These sufficient causes are state variables and in this case they may include Simvastatin, diet(citrus), genetics, age, diabetes, kidney dysfunction, infections, antibiotics, other drug interactions as well as idiopathic onset (Sauret, Marinides, & Wang, 2002). Simvastatin and grapefruit are part of the criteria related to this patient's health, but we have not captured all of the state variables associated with the development of rhabdomyolysis. Multiple variables have to align at the same time in order for this patient to

Box 1

State dependence in nonlinear dynamical systems. A nonlinear dynamical systems approach assumes that not all systems are separable and appropriately viewed as independent components with fixed relationships. Each psychosocial measurement, workload measurement, etc., collected from an athlete over time is a coordinate in a “state space” which forms the system. Each variable in the state space has its own axis. Munch, Brias, Sugihara, and Rogers (2019) explain that “a point in the state space corresponds to the current state of the system and the location of this point changes through time according to the rules governing the system dynamics. (Munch et al., 2019) This traces out a trajectory ... where, depending on the location in state space, pairwise relationships among coordinate variables may change through time.” When we refer to the “state” of a system we are using a tool from nonlinear dynamics to refer to the location of the system along a trajectory of observations. (Giron-Nava et al., 2017; Jiang et al., 2018) Nonlinear dynamics can be useful when we cannot measure all of the variables that describe the dynamics of a system but we would still like to have an idea of how that system might behave over time. Suppose we are studying the dynamics of a hypothetical athlete's weekly average performance and ACWR (which occasionally exceeds 2.0). The full state space (for simplicity) are the scores of both measures. Now, imagine that the dynamics exhibit a fairly simple cycle in which performance quality increases when ACWR is lower and decreases when ACWR is high. If we have data on the current measures of both performance quality and ACWR, there is no ambiguity in how each measure will likely change. However, if all we know is the current performance quality (red dot), we will have an equal number of observations of performance improving (left arrow) and performance decreasing (right arrow). Performance quality will appear as a ‘sharp cause’ of match readiness. On the other hand, if we know in addition to the current player performance measurement, that the performance quality now is greater than it was a few days ago, then we must be on the left side of the loop. As a result of including this additional information, we can predict that the performance will continue to increase following the usual training schedule. Moreover, we can infer that ACWR is currently low and likely to increase, given the historical training schedule.



develop rhabdomyolysis. Eating a grapefruit at least 12 h before taking a statin may decrease the harmful effects. The potential benefits or negative side effects of Simvastatin will, in addition to other state variables, be dependent on both when and how much (*timing and magnitude*) grapefruit juice is ingested relative to when and how much medication is taken.

This is an example of a *state dependent* relationship. If we're wondering whether grapefruit juice can be harmful, the answer for this patient is: it depends on when or in what context we're asking. If the state of their system includes very recent ingestion of Simvastatin and the amount of juice consumption is large enough, close in time to the ingestion of the Simvastatin and other sufficient causes are present during this period then the answer is, yes, grapefruit juice may be harmful. But, if they have not taken Simvastatin for over a month, this patient could consume the exact same amount of grapefruit juice and the juice would not be harmful. State dependence is common in biological systems and is a fundamental property of nonlinear systems (Adams, Berner, Davies P, & Walker, 2017; Deyle et al., 2013; Doiron et al., 2016; Grziwotz, Strauss, Hsieh, & Telschow, 2018; Kubin, 2016; May 1976; Sugihara et al., 1996, 2012). Just as spurious correlations can lead one down the path of testing imaginary relationships (i.e. false positive or type I error), the absence of correlations or contradictory correlations can lead one to dismiss real relationships that require deeper investigation into missing explanatory variables (i.e. false negative or type II error).

1.2. State dependence

In a state dependent system, interactions between variables aren't static. They change as the system changes and sometimes they can be correlated, sometimes anti-correlated and sometimes those same variables may not appear to be related at all, depending on the state of the entire system. In these systems the relationship between two variables depends on other variables (Chang, Ye, & Miki, 2020).

As another example of what is meant by state dependence,

research by ecologists illustrates that the water in a lake may remain absolutely clear, unaffected by slowly growing amounts of nutrients until suddenly, the state of the lake shifts and the water becomes murky (Scheffer, Carpenter, Foley, Folke, & Walker, 2001). The relationship between fish, zooplankton, phytoplankton and lake clarity depends on many factors, including the dimensions of the lake, the climate and nutrients. The role of fish in this ecosystem varies depending on the state of the lake. Increasing numbers of fish do not always lead to increasing health of a lake. Fish can be helpful in maintaining the health of a clear lake, but when the water is murky, fish impede the return of clarity by stirring up sediment and preying on zooplankton which eat phytoplankton, all of which makes it difficult to bring the lake back to the clear state. Although the fish were helpful when the lake was clear, removing the murkiness from the water requires temporary large reductions in the number of fish in the lake. In sum, the interactions between fish, plankton and plant life change depending on the state of the lake. The model of lake dynamics might also apply to athletic injuries.

Attempts to establish a relationship between dynamic knee valgus on performance tests and ACL tear have met with mixed results (Fox, Bonacci, McLean, Spittle, & Saunders, 2016). Bahr (2016) effectively showed that when we examine the ability of tests to predict ACL injury using knee abduction moment there is substantial overlap between athletes who do and do not become injured over time after demonstrating poor dynamic knee valgus control during testing. The overlap results in poor correlation between external knee abduction moment during testing and likelihood of suffering an ACL tear (Bahr, 2016). Statistical models assume the relationship between variables is fixed over time and deviations from the model (an athlete who has a positive test but who does not suffer an ACL injury) are often treated as random noise. Another possibility is that a change in landing strategy does not exert a constant multiplicative/linear effect such as we might see if an increase in dynamic knee valgus of 2° always doubled the likelihood of injury. Bittencourt and colleagues suggest that the determinants (state variables) leading to an ACL injury are numerous and can vary depending on the type of activity (Bittencourt et al., 2016). In other words, an ACL injury may also be state dependent – the state space (values and relationship between variables) of an athlete's injury resilience at one snapshot in time may be sufficient to resist ACL failure during an exposure to an activity, but the ACL fails when exposed to a different activity or the

same activity at a different time when the state of the variables has changed. While poor drop jump test results may not reflect a direct cause of ACL failure, those results may be indicators that knee abduction moment is a state variable which influences the likelihood of an ACL injury but is state dependent and driven by other internal and external factors.

In a system which is state dependent, a variable can exhibit very different causal effects, protective or destructive, depending on the timing and magnitude of the variable (Sugihara et al., 2012). In Fig. 1 we illustrate how this might appear using results from a number of studies (Cross, Williams, Trewartha, Kemp, & Stokes, 2016; Dennis, Farhart, Goumas, & Orchard, 2003; Gabbett, 2016; Sampson, Murray, Williams, Sullivan, & Fullagar, 2019; Williams et al., 2017). For example, cricket bowlers who rested 3–4 days between outings demonstrated a decreased risk of subsequent injury versus those who rested more than or less than that time period (Dennis et al., 2003). The authors suggest that this may have been a protective effect of throwing regularly which was diminished when throwing became too infrequent.

Fig. 1 demonstrates risk as a state-dependent function that is increasing at both ends of the graph and decreasing or low in the middle. This U-shape curve is prevalent in studies examining injury in sport (Cross et al., 2016; Dennis et al., 2003; Gabbett, 2016; Sampson et al., 2019; Williams et al., 2017). Injury resilience includes a healthy state and an injured state. Variables are very distinctly different in the two states and we could imagine as the colors in the figure above change the system is approaching a tipping point beyond which there is a transition to a different state. This kind of tipping point is similar in all kinds of physical and biological systems.

Similar to the cricket example above, we also see the protective effect of throwing regularly and the U-shape relationship in baseball (Lyman et al., 2001). Young athletes who threw a large number of pitches in baseball over the course of a season were more likely to suffer an injury, as were athletes who threw too few pitches. We see a similar state dependent increase in injury risk for rugby players who participated in too few or too many matches over a 12-month period (Williams et al., 2017). This U-shaped injury risk curve persists across sports and activities (Gabbett, 2016; Sampson et al., 2019). In a system that is state dependent, the effect one variable has on another variable changes as the variables change over time. If we were to model this system, the different components could not be treated independently as the variables have

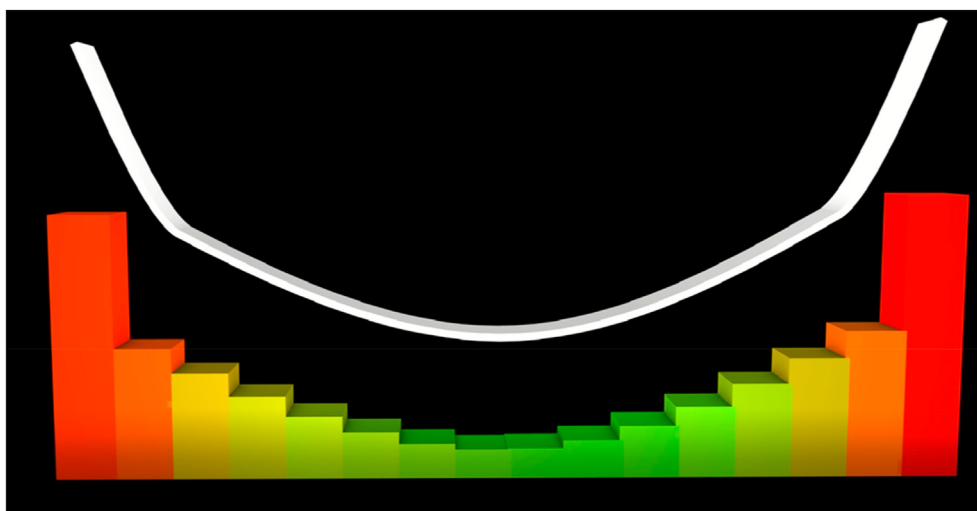
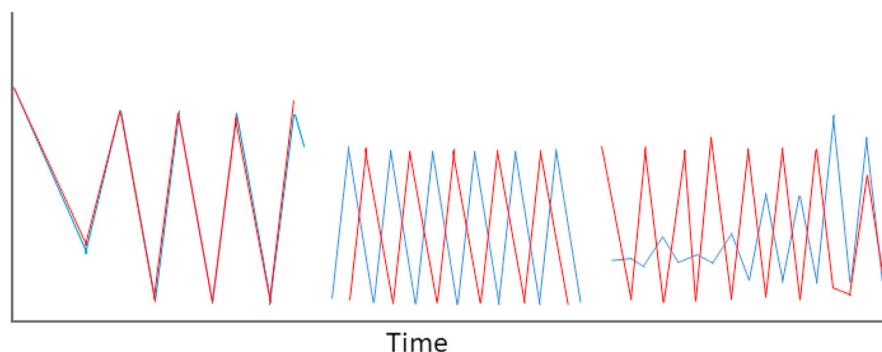


Fig. 1. "U"-shaped (non-monotonic) injury risk. Risk is represented by the vertical axis.



This behavior occurs in an ecosystem model of nonlinear dynamical systems. Initially the two variables are correlated, then they move in opposite directions and in the third time period the two variables no longer appear related.

Sugihara G et al. Detecting causality in complex ecosystems. *Science* 2012;338:496-500.

Fig. 2. Mirage correlations.

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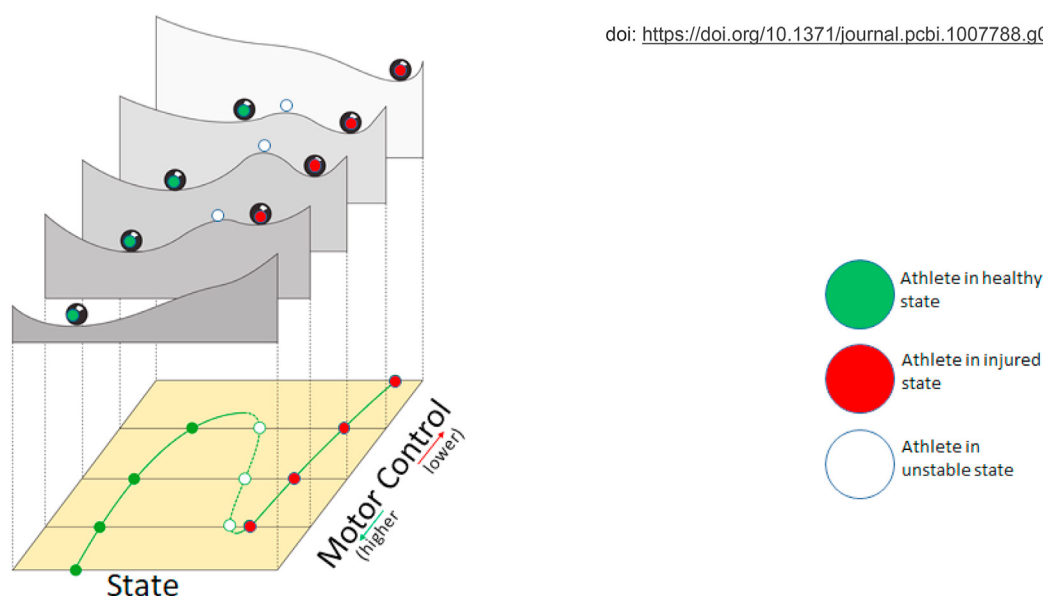


Fig. 3. This theoretical model demonstrates that below or above a threshold of motor control scores a tipping point is encountered and risk of injury shifts dramatically. There are two stable states – healthy and injured – and the white marbles indicate an unstable region where an athlete may shift between injury and healthy states more easily. Viewing the marbles on the “stability landscape” above the graph, as motor control construct scores increase the slope of the landscape shifts and the athlete becomes more likely to remain in the stable healthy state. As motor control construct scores decline the landscape shifts in the opposite direction and remaining in the healthy state becomes more difficult. (Rodríguez-Sánchez, van Nes, Scheffer, & Climbing Escher’s stairs, 2020; Scheffer et al., 2001)

interdependent effects (workload and injury may affect each other, but a third variable such as weather or days of rest could drive *both* workload and injury).

The “Butterfly Attractor” in Video 1 comes from a fluids model in physics. We use this model here to illustrate how variables X, Y and Z are positively correlated in one lobe and negatively correlated in the other, showing the relationship between these variables changing over time. We can imagine the variables rest, overhead deliveries and injury risk, competing and interfering with each

other over time in a similar pattern. Like our Simvastatin example, this is not a simple correlation or linear relationship as days of rest and the number of overhead deliveries can have both positive and negative implications for risk of future injury. Looking at the mean would not provide the best representation of the relationship between deliveries and risk of injury or rest and risk of injury. A ‘mirage correlation’ occurs when two variables which have shown a positive relationship with each other over a period of time suddenly become decoupled or anticorrelated (Fig. 2).

1.3. Mirage correlations: Does past injury predict future injury or is there another explanation for this relationship?

We also find evidence of state dependence in the relationship between motor control and likelihood of future injury: there is evidence that a prior injury influences the likelihood of future injury to a greater extent when motor control is impaired (Hegedus et al., 2016). Measuring the constructs of motor control and hip stability may explain the predictive value and dynamic relationship between past injury and future injury. With excellent motor control construct scores past injury provides little predictive value with regards to future non-contact injury when we account for state dependence (Fig. 3).

Fig. 3 is a theoretical model based on the work by Hegedus et al. describing the relationship between motor control and injury (Hegedus et al., 2016). The structure of the figure is from a bifurcation diagram describing ecosystem dynamics of a bistable system as the water in a lake reaches a threshold or tipping point and shifts rapidly from clear to murky (Rodríguez-Sánchez, van Nes, Scheffer, & Climbing Escher's stairs, 2020; Scheffer et al., 2001). The top section is a “stability landscape” where the slope of the landscape represents the underlying dynamics of the system. For example, the marble on a peak is in an unstable area, while the marble in a valley is quite stable. The slope of the surface is proportional to the rate at which the state of the system will change. In the Hegedus et al. data athletes with lower motor control construct scores tended towards higher risk of injury and athletes with higher motor control scores had a lower risk of injury. As Scheffer et al. (2001) note, “represented by the (white marbles) between the two thresholds, the system is bistable”. This bistable area of the system (white marbles) is where two different states - injured and healthy - are possible under the same motor control scores. One interpretation of the Hegedus et al. study is that the effect of a prior injury on the likelihood of being injured in the future depends on the state of the motor control construct score and a dichotomous ‘yes’ or ‘no’ value for prior injury will not provide us with sound management decisions for our athletes.

In a state dependent system, causation in some past time period can produce a response at one or even multiple different time

periods. Like the flexible cord on a light fixture, a prior injury can pull down the quality of motor control, but it cannot push it up. Esarey and colleagues found that in a state dependent system, the effect of an independent variable (x) on a dependent variable (y) at a given time (t) depends on the prior value of the dependent variable ($y(t-1)$) (Esarey & DeMeritt, 2017). Poor motor control scores may be meaningful with regards to the risk of future non-contact injury among athletes who have a history of higher relative risk of suffering non-contact injuries (Meeuwisse, 1994). An athlete's relative risk of suffering an injury increases if they are predisposed via internal risk factors or susceptible via external risk factors. In this sense, the relationship between motor control (x) and increased relative risk of non-contact injury (y) is a function of the state of past relative risk of non-contact injuries ($y(t-1)$), not simply whether or not the athlete has been injured once in the past. We should discriminate between the variables “relative risk for non-contact injury” and “prior injury”. Sometimes a prior injury is indicative of a history of a high relative risk, but this is probably not always the case.

Although motor control influences the likelihood of an injury, an injury will also impact the quality of motor control. An athlete suffering an injury will likely have altered motor control construct scores and without appropriate intervention to return motor control to optimal levels, the likelihood of future injury will be increased (Gokeler, Neuhaus, Benjaminse, Grooms, & Baumeister, 2019). If we do an excellent job rehabilitating our athlete after an injury, bringing them to a condition that exceeds even their baseline, we may even see a negative relationship between prior injury and likelihood of future injury (Fig. 4). Over short periods, suffering an injury may influence the likelihood of future injury, but through appropriate rehabilitation the relationship between prior injury and likelihood of future injury changes.

1.4. Injury risk: Our athlete as a state dependent system

Annual sales of fish are approximately U.S. \$80 billion and quotas for harvesting those fish from U.S. waters are set each year based on predictions of fish stock size (Dalton, 2005). For years

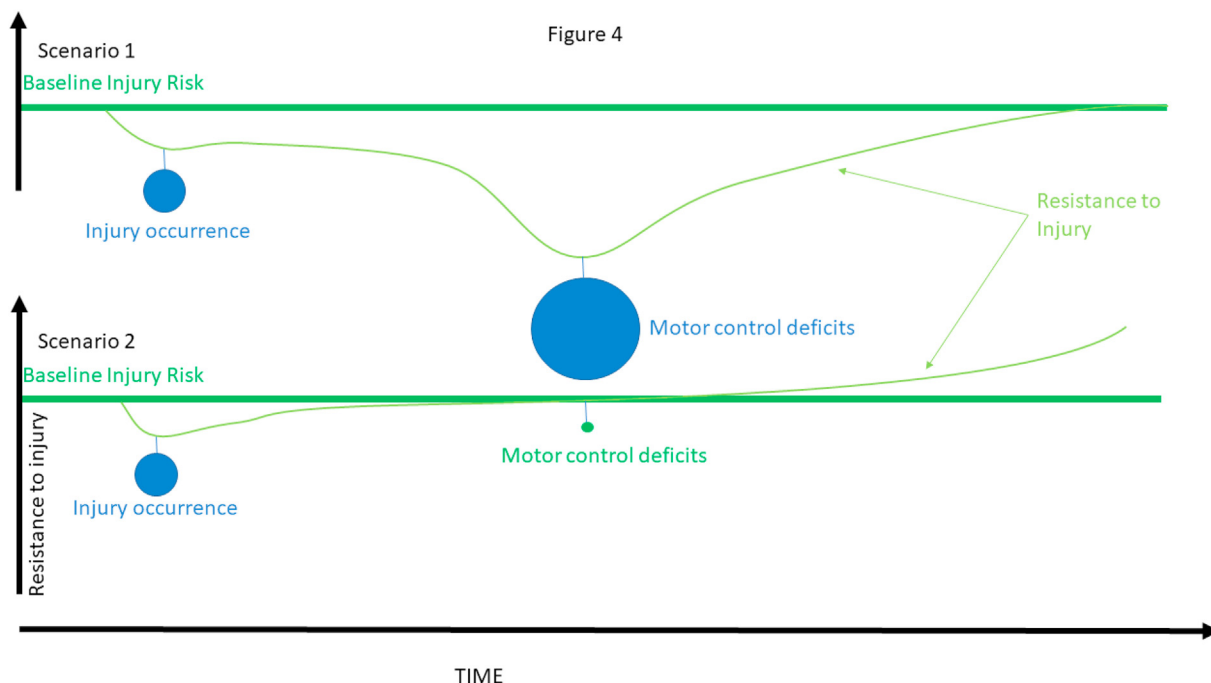


Fig. 4. The effect of prior injury on likelihood of suffering an injury in the future is state-dependent. Rehabilitation of motor control deficits, for example, alters this relationship.

individuals hypothesized that the reciprocal abundance of sardines and anchovies in the Pacific was a result of competition between the two species along with large changes in the environment (Sugihara et al., 2012). Assuming those relationships, parametric models were developed and used to guide the fish harvest. However, from 1992 to 2009 the relationship between sardine recruitment and the environment disappeared – a mirage correlation consistent with nonlinear systems. Investigating the cause using nonlinear models which take into account state dependence showed that sardines and anchovies were not in fact interacting. Instead of competition with each other, sea surface temperature was a common driver of anchovy and sardine abundance.

Even when we know some of the causal variables, including them in improperly formulated models will produce conflicting results. People argued for years over the impact of competition between anchovies and sardines and given that this was all of the data they had it did not seem like an unreasonable argument at the time. Examining temperature as a state dependent variable helped clarify that temperature was the real driver of the system. We can assume that the number of variables needed to completely characterize the system dynamics leading to non-contact failure of an ACL could be unbelievably large or seemingly infinite. In experimental situations one can only measure a finite number of these variables and often only a few of these variables are collected over time in an athlete. With a single (or a few) measured time series, similar to the hypothetical example in Box 1, it is possible to characterize the dynamical behavior and identify state dependence using methods from nonlinear dynamics such as delay-coordinate embedding (Takens, 1981).

An athlete is a system and the status of all of the factors that provide resistance to injury at one snapshot in time is considered the state of the system. The examples above illustrate that the order of events and the interdependence of variables are relevant as these relationships vary depending on the state of the system. In ecological research factors are said to be weakly or moderately coupled when the relationship between them is not consistently positively or negatively correlated over time. Weak associations between factors, such as those occurring between prior injury and risk of future injury or days rest and relative risk of future injury as a result of other driving variables, such as motor control or number of pitches, leads to the appearance of transient relationships between factors. This can make deciding whether a relationship is meaningful or deceptive difficult. We assume that the effect of one variable on the other is constant and if we remove that variable that the other will return to baseline. But that reasoning does not capture the dynamics of the system.

In a previous paper we explored how the rapid changes and interactions between variables makes it very difficult to predict which athletes are likely to suffer an injury using pre-season screens (Stern et al., 2020). State dependence offers a way to think about the contrasting injury prevention evidence and how to synthesize better understanding of resistance to injury. We hope this paper helps to guide future studies by creating the skeleton or a mental framework with which context-dependent mechanisms can be evaluated as working together or in opposition, or in evaluating the strengths of different interactions. Just as the effect of rest, throwing or Simvastatin may vary from protective to destructive or knee abduction moment or a history of injury may or may not provide useful information with regards to future injuries, we should be wary of giving equal weight to a variable regardless of the system state (Sugihara et al., 2012). In circumstances where there is not a well defined cause and effect, the more of a role nonlinear dynamical methods play the better we will understand these relationships. Using a nonlinear dynamics approach provides an opportunity to look at other contributions to predictions. With

respect to identifying which athletes are susceptible to non-contact injuries we may know as much as we can know from the models we have designed to date. Let's look at something new.

Ethical statement

This work did not involve the use of animal or human subjects.

Declaration of competing interest

We have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pts.2021.01.008>.

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