Understanding thermoregulatory transitions during haemorrhage by piecewise regression

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Abstract. Transition points are common in physiological processes. However the transition between normothermia and hypothermia during haemorrhagic shock has rarely been systematically quantified from intensive time series data. We estimated the critical transition point (CTP) and provided confidence intervals for core body temperature response to acute severe haemorrhage in a conscious rat model. Estimates were obtained by traditional piecewise linear regression (broken stick model) and compared to those from the more novel bent cable regression. Bent cable regression relaxes the assumption of an abrupt point transition, and thus allows the capture of a potentially gradual transition phase; the broken stick is a special case of the bent cable model. We calculated two types of confidence intervals, assuming either independent or autoregressive structure for the residuals. In spite of the severity of the haemorrhage, median temperature change was minor (0.8 °C; IQR 0.57-1.31 °C) and only four of 38 rats were clinically hypothermic (core temperature < 35 °C). However, a transition could be estimated for 23 rats. Bent cable fits were superior when the transition appeared to be gradual rather than abrupt. In all cases, assuming independence gave incorrect uncertainty estimates of CTP. For 15 animals, neither model could be fitted because of irregular temperature profiles that did not conform to the assumption of a single transition. Arbitrary imposition of broken stick fits on a gradual transition profile and assuming independent rather than autocorrelated error may result in misleading estimates of CTP. Identification of the onset of irreversible shock will require further quantification of appropriate time-dependent physiological variables and their behaviour during haemorrhage.
Introduction

Transition points are common in physiological processes. Frequently, physiological responses to specific stressors will be nonlinear, with a critical threshold occurring when the response is believed to change more or less abruptly at some level of the independent variable. This critical transition point (CTP) is indicative of a change in physiological state, and therefore may serve as a marker of that state change. Such changes may be relatively innocuous, such as the so-called lactate threshold (Myers & Ashley, 1997; Vachon et al., 1999) or the gas exchange threshold (Kelly, 2001), which are associated with the transition from aerobic to anaerobic metabolism. In other cases, transitions indicate an undesirable pathological state change that may be impossible to reverse. One example is the transition from a state of compensated to decompensated shock, where oxygen extraction by the tissues is no longer sufficient to meet demand, resulting in ischemic metabolic insufficiency (Schumacker & Cain, 1987; Schumacker & Samsel, 1989), accumulation of oxygen debt (Dunham et al., 1991; Barbee et al., 2010), and increased risk of mortality. It is of great clinical importance to be able to identify early signs of shifts in regulated physiological functions that forecast the risk of abrupt pathological change. This is analogous to the problem of forecasting regime shifts in ecological systems. Unfortunately, both types of regime shift share a common problem: the only certain identifier of a regime shift threshold is to cross it (Thrush et al., 2009).

Nevertheless, accurate quantitative descriptions of the transition region are an essential first step to elucidating mechanisms underlying the change (Connett et al., 1986).

Hypothermia is common following traumatic injury and is a significant risk factor
for acidosis, coagulopathy, and mortality (Peng & Bongard, 1999; Tsuei & Kearney, 2004; Martini, 2009). There is considerable debate as to whether hypothermia is a relatively late sign in the development of shock (Peng & Bongard, 1999; Smith & Yamat, 2000; Beilman et al., 2009), or is a complication independent of the shock process (Silbergleit et al., 1998). Clinical studies rarely distinguish between environmentally-induced hypothermia – that is, hypothermia induced by aggravated heat loss occasioned by CNS injury, intoxication, treatment interventions such as fluid resuscitation, etc. (Luna et al., 1987) – or hypothermia as a marker of progressive metabolic dysfunction (Beilman et al., 2009). To add to the confusion, spontaneous core temperature reduction occurs during haemorrhage in laboratory animal models; and in this context is actually a regulated autonomic change acting to reduce metabolic rate, and thus tissue oxygen demand, as oxygen delivery becomes progressively more limited (Henderson et al., 2000; Brown et al., 2005). The extent of the temperature change may also depend on the amount and rate of blood loss during haemorrhage (Connett et al., 1986; Wu et al., 2003). Data-driven models of body core temperature over time have been used as “early warning” indicators of heat-related pathological change during intense activity (Gribok et al., 2006; Gribok et al., 2007; Gribok et al., 2008). However, patterns of body temperature change during haemorrhage have not been examined for their utility in early prediction of the onset of decompensated shock. This may be partially because core temperature reduction during haemorrhage in laboratory rodents is relatively minor – less than 1°C (Henderson et al., 2000) to approximately 2°C (Brown et al., 2005) – so that detection of the transition region is difficult until core temperature depression becomes pronounced.
This study examined an intensive time course of individual thermoregulatory patterns during controlled severe haemorrhage in a conscious rat model. Because core temperature depression was expected to be relatively subtle, the goals were first, to determine if early-stage thermoregulatory transition could in fact be detected, and second, to determine the most biologically meaningful and best-fitting model of that transition for each individual subject. Model reliability was assessed by comparing the performance of two competing piecewise regression models: the conventional broken stick model (Vieth, 1989; Berman et al., 1996; Toms & Lesperance, 2003) versus the bent cable model (Toms & Lesperance, 2003; Chiu et al., 2006; Chiu & Lockhart, in press) as descriptors of the transition region. We also assessed the effect of correlation between sequential observations on the precision of the change point estimate.

Methods

Ethical approval. This study was approved in advance by the Institutional Animal Care and Use Committee (IACUC) of Virginia Commonwealth University, and conforms to the Public Health Service Policy on Humane Care and Use of Laboratory Animals (2002).

Animal husbandry. Male Long Evans rats were obtained from Harlan Laboratories (Indianapolis IN) at approximately 8 weeks of age. Prior to experimentation, animals were housed two to a cage and maintained at 25 (SD1) °C and 12L:12D in the animal colony. All rats had access to food (commercial rat chow) and water ad lib. Rats weighed an average of 314 (SD 12) g at the time of experiments.
Core temperature and haemorrhage data. Data reported here were collected as part of a study designed to assess resuscitation strategies in a conscious rodent model that best promote survival for 3 h following severe (60% total blood volume) haemorrhage without conventional large-volume crystalloid support. Study guidelines were directed by the Defense Advanced Research Projects Agency [DARPA] [no. BAA04-12; http://www.darpa.mil/baa/baa04-12mod3.html]. Haemorrhage and resuscitation procedures have been described in detail elsewhere (Reynolds et al., 2007) and are briefly summarized here.

Rats (n = 38) were anaesthetized with isoflurane (5% for induction, 1%–2% for maintenance, balance O₂). During surgery core temperature was monitored with a rectal probe and maintained at 36.5–37.5°C with a thermostatically controlled feedback heating blanket (Harvard Apparatus, Holliston, MA). Animals were catheterized and implanted with an intraperitoneal temperature transponder (Emitter; Minimitter, Bend, OR) under surgically sterile conditions, then allowed to recover from anaesthesia for 30-60 minutes before haemorrhage began, after they were able to both right themselves and maintain a sternal position. This delay ensured adequate time for anaesthetic gas washout. For pain control, all incisions and routing tracks were coated with topical 2% lidocaine gel. An unprimed micro-osmotic pump (model 1003D; Alzet Osmotic Pumps, Durect, Cupertino, CA) filled with morphine (50 mg mL⁻¹) was implanted subcutaneously at the nape to deliver approximately 0.15 mg kg⁻¹ h⁻¹ morphine after haemorrhage; animals also received a single SQ morphine injection (0.3 mg kg⁻¹).
Animals were haemorrhaged from the carotid catheter in three 20%-volume increments at rates of 1.0, 0.5, and 0.25 mL min\(^{-1}\), respectively. Blood was withdrawn by a programmable syringe pump (PHD22/2000 Series, Harvard Apparatus, Holliston MA). Blood draw was constrained by a minimal mean arterial pressure (MAP) threshold of 40 mm Hg. If MAP fell below this threshold, haemorrhage was stopped and animals were then allowed to auto-resuscitate until a MAP of 40 mm Hg had been maintained for at least 75 s, after which haemorrhage was resumed until target shed blood volume (SBV) was achieved. Target SBV was calculated as 60% of the total blood volume (TBV), which was estimated from body mass of each subject as TBV (mL) = 0.77 + 0.06 \((\text{mL/g}) \cdot \text{M}\), where M is body mass (g) (Lee & Blaufox, 1985). Blood volumes removed averaged 11.8 (SD 0.5) mL. Animals were then resuscitated with one of four fluid treatments as described previously, and monitored for 180 min or until cardiac collapse. Two rats did not survive to receive the full resuscitation intervention. Animals surviving to 180 min were humanely euthanized with Euthasol (pentobarbital, 0.3-0.4 mL kg\(^{-1}\) or 100-150 mg kg\(^{-1}\), IV) (Reynolds et al., 2007).

Core temperature was logged by remote data collection for the duration of each trial, and averaged at 15 s increments (“time steps”) using an exponentially-weighted moving average algorithm (VitalView® Data Acquisition System; Minimitter Inc., Bend, OR). Temperature records for each animal were between 127 and 246 time steps (32 to 62 min) long, and for this analysis included only the haemorrhage portion of each trial.
Models. Numerous quantitative or model-based approaches have been proposed for identifying physiological thresholds; however the most common is to fit a piecewise linear regression model (Berman et al., 1996). Piecewise regression models consist of two or more time trajectories of a physiological response, characterized as either lines or curve segments joined at a point that typically represents the transition. The transition may occur because of either a specific experimental or quasi-experimental intervention (Gillings et al., 1981) or a physiological state change (Schumacker & Cain, 1987; Vieth, 1989; Berman et al., 1996; Myers & Ashley, 1997; Vachon et al., 1999). Typically, the process is modelled as two separate straight lines with different slopes and a common intersection point at the transition point $\tau$ (Fig. 1; Vieth, 1989; Berman et al., 1996); this is sometimes referred to as the broken stick model (Toms & Lesperance, 2003).

The broken stick model describes a single time course of core temperature data as:

$$y_t = \begin{cases} 
\beta_0 + \beta_1 t + \epsilon_t & \text{for } t < \tau \\
\beta_0 + \beta_1 t + \beta_2 (t - \tau) + \epsilon_t & \text{for } t \geq \tau 
\end{cases}$$

(1)

where $\beta_0$ is the baseline core temperature, $\beta_1$ is the rate of temperature change before the transition point $\tau$, $\beta_1 + \beta_2$ is the rate of temperature change after the transition point $\tau$, and $\epsilon_t$ is the regression error, or residual, at time $t$. The model is constrained by the intersection of lines at $\tau$; this point is unknown and must be estimated from data. Here, the critical transition point CTP is equal to $\tau$.

Although convenient and easy to implement, estimates derived from the broken
stick model may be compromised by the scientifically uncritical assumption of an abrupt
transition point. Not only may this model lack theoretical justification, in many cases it
may not even resemble the actual data (Jones & Handcock, 1991; Routledge, 1991;
Myers & Ashley, 1997). For many transition series, a more realistic model may be the
bent cable regression model (Chiu et al., 2006; Chiu & Lockhart, in press). Here, the
data are described in terms of two linear segments as before, but the transition between
the two segments is modelled as a quadratic bend (Tishler & Zhang, 1981), such that
(Fig. 1). Here \( \gamma \) is a non-negative parameter that determines the width of the quadratic
transition zone that is centred at \( \tau \) and ranges from the lower bound at \((\tau - \gamma)\) to the
upper bound at \((\tau + \gamma)\). Unlike the broken stick model, the bent cable model is smooth
with no obvious change point. Instead, the transition is more accurately characterized
as the range of time over which the trajectory has a positive slope, followed by the time
range where core temperature declines and the trajectory has a negative slope.
Therefore CTP occurs where the slope of the trajectory inside the quadratic bend is
equal to 0, so that the CTP is \([\tau - \gamma - (2{\beta_1\gamma}/{\beta_2})]\). However if \( \gamma = 0 \), the model reduces to
Eqn. 1 and CTP equals \( \tau \); therefore, the broken stick model is a special case of the bent
cable model (Chiu et al., 2006).

**Autocorrelation.** One key assumption of common regression-type models is that the
residuals \( \varepsilon_i \)s are independent of each other. However, with time series data, these
residuals are usually correlated over time; the correlation between sequential
observations is \( \rho \). If this autocorrelation is ignored (that is, \( \rho \) is naively assumed to be equal to zero), width of the confidence intervals will be misleadingly narrow. In practical terms, when the value of one measurement influences the determination of another, then the information available from these two measurements combined is less than that obtained from two independently-observed measurements. Therefore, this autocorrelation must be accounted for in the model.

When time intervals are equally spaced, an autoregressive (AR) structure for the residuals is often adequate; AR models are appropriate when it is reasonable to assume that any currently-observed value of the series depends on immediate past values, plus a random error component. Thus, the autoregressive component is a linear regression of the current value of the residual at time \( t \) \((\varepsilon_t)\), where the independent variables are the \( p \) previous values of the time series \( \varepsilon_{t-1}, \varepsilon_{t-2}, \ldots, \varepsilon_{t-p} \). The quantity \( p \) is the “order” of the autoregression, and is a measure of the amount of memory in the system. For example, an autoregressive series with \( p = 3 \) means that the current value of the series is dependent on its previous \( p = 3 \) lagged values, and is said to have an AR(3) structure. If there is no autocorrelation between observations (i.e. the series is white noise) then \( p = 0 \). In general, the autocorrelation between sequential observations \( y_t \) is expressed in terms of autocorrelated residuals as

\[
\varepsilon_t = \varphi_1 \cdot \varepsilon_{t-1} + \varphi_2 \cdot \varepsilon_{t-2} + \ldots + \varphi_p \cdot \varepsilon_{t-p} + \delta_t \tag{3}
\]

where \( \varphi_1, \ldots, \varphi_p \) are the AR coefficients to be estimated, and \( \delta_t \)s are the uncorrelated autoregression errors (or white noise) with variance \( \sigma^2 \). If \( p = 0 \), then \( \varepsilon_t \) reduces to white noise \( \delta_t \) (Box et al., 1994). Based on asymptotic statistical properties of the conditional
likelihood function (Chiu & Lockhart, in press), the 95% confidence interval for CTP can be approximated as the estimated value of CTP $\pm [1.96 \cdot (\bar{\xi}' V \bar{\xi})^{1/2}]$, where $\bar{\xi}'$ is the row vector $[0, -2 \cdot \gamma/\beta_2, 2 \cdot \beta_1 \cdot \gamma/\beta_2^2, 1, -(2 \cdot \beta_1 + \beta_2)/\beta_2]$, and $V$ is the 5 x 5 asymptotic covariance matrix for the vector of estimated bent cable regression coefficients, obtained from Eqn. 2.

**Model fitting.** The model fitting process consisted of three steps. First, preliminary structural model fits were obtained separately for each subject. Because the broken stick model is a special case of the bent cable model, the broken stick fit was obtained by constraining $\gamma = 0$; to obtain the bent cable fit, this constraint was removed. In this preliminary model a “naïve” fit was obtained by assuming independent errors (i.e. $p = 0$). Second, we obtained the residuals from this preliminary model and applied standard autocorrelation diagnostics (ACF, PACF) to determine the order $p$ of the autoregression (Box et al., 1994); this value for $p$ was substituted in Eqn. 3. Finally parameters for the full model (i.e. $\sigma^2$ and all unknown coefficients from Eqn. 2 and 3) were simultaneously estimated by conditional maximum likelihood (Chiu & Lockhart, in press). Because there is no analytical solution, goodness of fit was assessed by visual inspection of the fitted curve and residual diagnostics (Fig. 2). If the tentatively-entertained model is correct, then plots of $\xi_t$ over time should exhibit mean 0 and constant variance with no heteroscedasticity and no departure from randomness (Box et al., 1994). Six data series required minor trimming of data ($< 10$ data points) on either end of the sample period to allow model convergence and sensible estimation of model parameters. Model fitting was performed using the statistical computing software R with the bentcableAR
package; code is available online at http://www.r-project.org.

Results

In spite of the severity of the haemorrhage protocol, only four of 38 rats in this study showed signs of clinically mild hypothermia [core temperature < 35 °C; (Beilman et al., 2009)] at the end of haemorrhage; four were borderline (core temperature between 35-36 °C). Temperature of the remaining animals averaged 37.13 (SD 0.55) °C at the end of haemorrhage. The median difference between peak temperature and that recorded at the end of haemorrhage before fluid resuscitation (ΔT) was 0.8 °C (IQR 0.57-1.31 °C). However, although most animals were technically normothermic following haemorrhage, data for 23 animals showed a detectable transition in core temperature trajectory during haemorrhage (Table 1). For these subjects, there was reasonable within-subject agreement in estimates of the transition point. Estimated CTP averaged 17.5 and 16.1 min respectively for the broken stick and bent cable models with independent errors, and 17.7 and 15.5 min with autoregressive errors. For 9 subjects, the bent cable-autoregressive model was a better fit than the broken stick–autoregressive model (Fig 2.A); discrepancies between models in estimates of CTP were as large as 4 min in some cases.

When the estimate of γ was exactly or approximately zero, two technical complications resulted. First, estimates of CTP from the bent cable model (Eqn. 2) were often (although not always) virtually identical to the broken stick model (Eqn. 1; Fig. 2.B); however because γ = 0, the resulting confidence intervals for the estimate were
degenerate. A different type of degeneracy resulted from bent cable fits where the slope never changed sign, so that CTP is undefined and the corresponding confidence intervals could not be computed. For subjects where CTP estimates were virtually identical between methods, visual inspection of graphics and residuals (Fig.3) suggested the most appropriate model fit.

For all 23 series, the data showed statistically significant correlation. The autoregressive order $p$ was between 2 and 4 for 19 cases, and between 5 and 7 for four cases (Table 1), indicating a time-dependent “persistence” (Santer et al., 2008), or lag, of between 30 sec to almost 2 min. When autoregressive error was incorporated into the full model, confidence intervals from broken stick fits were substantially narrower than those from bent cable fits (Table 1). Estimates of CTP obtained from broken stick models appeared to be sensitive to the accounting of autocorrelation in the error structure. This was suggested by the observation that in many cases CTP and corresponding confidence intervals differed considerably between models incorporating autoregressive errors (that is, $p > 0$) compared to those assuming independence ($p = 0$; Table 1).

For 15 cases, no single CTP could be clearly identified because temperature profiles were too irregular or oscillatory to allow a reasonable fit by either model. Two examples are shown in Fig. 4. In the first case, relatively large-scale amplitude oscillations ($0.5 \, ^\circ C$) in core temperature began with the onset of haemorrhage and continued to haemorrhage cessation. In the second case, an initial $1^\circ C$ drop in temperature beginning approximately 6 minutes into the haemorrhage was followed by
damped oscillations around what may be a new reduced set-point (Henderson et al., 2000; Brown et al., 2005).

**DISCUSSION**

In this study we evaluated time-dependent patterns of body temperature regulation during haemorrhage in rats, with models assuming the existence of a defined transition between relative normothermia and the onset of core temperature depression. Methods were based on a regression model incorporating the novel use of bent cable regression (with its relaxed assumptions as to the smoothness of the transition region), together with parametric time-series models (to correct estimation problems associated with residual autocorrelation). Although only four animals could be considered technically hypothermic at the end of haemorrhage, threshold models could be fitted to data for approximately two-thirds of the subjects in this study. These data showed that even subtle changes in core temperature can be detected during intensive monitoring.

Shifts in physiological regulatory steady state as a result of some stressor are often described by thresholds (Vieth, 1989; Berman et al., 1996), critical points (Schumacker & Cain, 1987), deflection points (Vachon et al., 1999), or change points (Jones & Handcock, 1991; Berman et al., 1996; Kelly, 2001). Numerous studies have used piecewise regression models to estimate these transitions, e.g. (Schumacker & Cain, 1987; Vieth, 1989; Jones & Handcock, 1991; Samsel et al., 1991; Myers & Ashley, 1997; Vachon et al., 1999; Kelly, 2001). Many previous approaches have assumed that the transition is abrupt and clearly demarcated, and tacitly assumed that
the data on each subject consisted of independent observations (because potential
autocorrelation was not explicitly accounted for in the models). In this study, we
demonstrated that ignoring the shape of the transition region could affect estimates of
the transition time. Uncritical use of $\tau$ estimated from the broken stick model could
impede timely recognition of the transition recognition if an abrupt transition is assumed,
but the transition is actually gradual. Second, we showed that, if the correlation between
sequential observations is ignored, calculated confidence intervals are often
misleadingly narrow, giving a false impression of the precision of the estimates. In this
study, the assumption of independent and identically-distributed errors was not valid for
any subject. Although theoretical considerations suggest (and our data show) that
ignoring autocorrelation will in many cases yield estimates of $\tau$ and CTP consistent with
those obtained by incorporating autocorrelation in the final model, precision is greatly
affected by failure to incorporate appropriate error structure. Consequently, we consider
that autocorrelation between observations should be incorporated as part of the model,
and conditional maximum likelihood estimation applied for parameter estimation. If
within-subject autocorrelation is negligible or absent, the parameters of the broken stick
model can be estimated for each subject by using any standard nonlinear estimation
procedure, and confidence intervals for $\tau$ obtained using asymptotic standard errors.
However, for long data series sampled at frequent short time intervals, autocorrelation is
unlikely to be trivial, and these standard errors will not be reliable.

When autoregressive errors were incorporated into the models, confidence
intervals for CTP derived from broken stick fits were narrower than those from bent
cable fits. This result does not suggest that estimates derived from broken stick models are inherently less uncertain than the bent cable fits; rather this apparent “precision” is most likely an artefact of the more restrictive assumptions associated with the broken stick model. Specifically, when an abrupt breakpoint estimate is forced on a relatively smooth or gradual profile, the range of time steps required to bracket that estimate will be necessarily much smaller than those required for a smooth curve. In these cases, the broken stick fit could result in estimates of CTP and confidence intervals that poorly represent the observed profile.

Typically, effective fitting of autoregressive models requires at least a moderately long series; in general at least 50 observations are recommended (Box et al., 1994; Chatfield, 1996). In practice, this should be feasible if subjects are appropriately instrumented, and physiological data can be obtained as a single long intensive time series. In this study, data were sampled at extremely short (15 s) time intervals so that it was possible to capture the transition region and visually assess the adequacy of each model fit to the transition point.

To arrive at the actual “best” solution for a transition point requires a great deal of care, essentially consisting of an exhaustive search among the numerous “near-best” solutions for identifying the actual “best” solution. In a few cases, truncation or trimming a small number of data points at the end of the core temperature profile will allow sensible model fits. In this study, trimming was employed for six subject profiles (Table 1). However, model estimates may not be possible if the physiological profile for a given
subject does not exhibit a structure that resembles either biphasic model described here. For 15 cases examined in this study, no thermoregulatory transition could be clearly distinguished, and neither model provided a sensible fit. In these cases, mathematical irregularities of the regression arising from low-order differentiability will prevent estimation of model parameters (Chiu et al., 2002, 2005, 2006). These may occur because of excessive oscillations in the data series (Fig. 4). In these cases, even a statistical “best” fit may be nonsensical in practice because the postulated model does not provide an adequate description of the series behaviour. Oscillations in body temperature occurred either almost immediately after haemorrhage onset (< 20% blood volume removed) or appeared to be sustained around what may have been a new set-point (Brown et al., 2005) following more extensive blood loss (30-40% total blood volume; Fig. 4). Oscillatory instabilities in otherwise periodic (Mackey & Glass, 1977) or stable (Stark & Baker, 1959) physiological systems are common in many disease conditions (Mackey & Glass, 1977). Unstable oscillations in body temperature with haemorrhage may result from enhanced activity of, and feedback from, the sympathetic system, as is the case for arterial pressure oscillations during haemorrhage (Hosomi, 1978). Thus, uncritical use of any biphasic regression model is not recommended without visual inspection of the data beforehand.

If a transition region can be determined to exist based on external criteria, some otherwise intractable problems of individual model fits might be overcome by combining data for all individuals using a single longitudinal mixed-effects model. This will be appropriate if estimates of population characteristics, rather than subject-specific
quantities, are desired. For example, to compute the subject-specific transition point for each individual profile in this study there were five regression parameters ($\beta_0, \beta_1, \beta_2, \gamma, \tau$), plus $p$ autoregressive parameters and an error variance to be estimated. However, if all $n$ individual profiles can be considered collectively as a sample from a population, a single population cable profile with $(5 + p)$ unknown parameters, plus a handful of covariance parameters, could be estimated from the pooled data for all $n$ subjects; this leads to a single estimate of the population transition point. The two approaches differ because random between-subject variation is incorporated in the mixed-effects model (Khan et al., 2009; Khan et al., submitted), and could be useful for other physiological models.

Our method of estimating critical transition regions for individual subjects will be relevant to the study of virtually any dynamic physiological process characterized by a rate change in physiological state. In general, bent cable regression is a viable and preferred generalization of classic piecewise linear regression that allows for shape variability in the transition between phases. We recommend its use for situations where flexibility is desired, either because the underlying physiological mechanisms are not well understood, or where there is no strong supporting theory or evidence for a model of abrupt change in the transition between physiological phases. Because arbitrary imposition of broken stick fits on a gradual transition profile may result in very misleading estimates, broken stick fits should be avoided unless preliminary model estimation results in values of $\gamma$ that are near zero, indicating that a broken stick model is appropriate. Second, dependence between sequential observations cannot be
ignored. This is especially apparent in cases where a broken stick model is appropriate, as this model appears very sensitive to autocorrelation.

Early warning of a transition to physiological instability is highly desirable so that appropriate interventions can be performed before the subject is beyond help. Physiological monitoring devices have greatly improved in recent years so that extremely high-frequency sampling of variety of physiological variables is possible, enabling the generation of highly concentrated time series data over very short periods of time. This will allow the exploration of the behaviour of a wide variety of potential indicator variables. However identifying which of these variables can actually indicate incipient transition before the transition actually occurs is still difficult. Determination of such indicators will require both robust mathematical modelling and, more important, collection of long-term data series under carefully controlled conditions. Accurate estimates of time to this transition may serve ultimately to improve trauma management through better and earlier detection of shock and optimization of the timing and extent of therapeutic interventions.

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Table 1. Estimates of the critical transition point CTP of body temperature for 23 rats during severe controlled haemorrhage.

| Subject | Independent errors p = 0 | Autoregressive error |
|---------|--------------------------|----------------------|
|         | Broken stick | CI | Bent cable | CI | p | Broken stick | CI | Bent cable | CI | Y  |
| 1       | 24.71        | 1.65 | 24.30      | 2.29 | 2 | 23.63        | 0.87 | 23.63      | 0.79 | 0.00 |
| 2       | 15.87        | 1.23 | 14.80      | 0.69 | 3 | 24.25        | 0.53 | 14.80      | 1.24 | 10.31 |
| 3       | 19.10        | 1.38 | 19.02      | 1.49 | 7 | 17.86        | 0.50 | 17.86      | 2.57 | 0.00 |
| 4       | 19.12        | 0.90 | 15.92      | 0.78 | 5 | 16.38        | 0.44 | 15.82      | 2.06 | 9.69 |
| 5*      | 20.10        | 1.01 | 18.55      | 1.06 | 2 | 21.41        | 0.24 | 18.09      | 3.07 | 6.12 |
| 6       | 15.35        | 1.66 | 17.42      | 0.73 | 4 | 15.00        | 0.79 | 17.60      | 3.07 | 10.31 |
| 7*      | 15.43        | 0.36 | 13.69      | 0.58 | 6 | 16.92        | 0.10 | 14.84      | 1.22 | 1.28 |
| 8*      | 6.19         | 1.04 | 6.25       | 1.50 | 2 | 5.55         | 0.47 | 5.57       | 0.82 | 0.06 |
| 9*      | 9.70         | 0.80 | 9.81       | 0.58 | 3 | 10.24        | 0.42 | 9.92       | 0.94 | 3.91 |
| 10      | 12.18        | 0.68 | 13.11      | 1.77 | 4 | 11.55        | 0.55 | 13.51      | 3.86 | 3.04 |
| 11      | 15.63        | 0.83 | 12.41      | 0.45 | 3 | 23.28        | 0.39 | 12.43      | 1.41 | 9.69 |
| 12      | 4.91         | 0.87 | 5.89       | 1.65 | 4 | 6.63         | 0.43 | 6.64       | 2.06 | 0.00 |
| 13*     | 15.06        | 0.44 | 14.20      | 0.80 | 3 | 13.41        | 0.24 | 13.94      | 1.54 | 1.95 |
| 14      | 32.43        | 2.06 | .          | .    | 2 | 38.81        | 0.46 | .          | .    | 0.09 |
| 15      | 17.00        | 6.50 | 16.96      | .    | 3 | 17.75        | 1.44 | 17.75      | .    | 0.00 |
| 16      | 16.68        | 4.65 | 16.64      | .    | 3 | 22.50        | 1.54 | 18.49      | .    | 0.00 |
| 17      | 34.37        | 1.82 | .          | .    | 3 | 30.75        | 0.65 | .          | .    | 0.02 |
| 18      | 20.87        | 0.99 | .          | .    | 4 | 23.27        | 0.88 | 23.27      | .    | 0.00 |
| 19      | 12.52        | 1.05 | 12.50      | .    | 3 | 12.69        | 0.34 | 12.69      | .    | 0.00 |
| 20      | 36.92        | 1.16 | .          | .    | 5 | 38.90        | 0.14 | .          | .    | 0.24 |
| 21      | 20.15        | 0.77 | 20.15      | .    | 2 | 15.50        | 0.33 | 15.50      | .    | 0.00 |
| 22*     | 11.60        | 2.05 | 11.00      | 6.12 | 3 | 19.75        | 0.37 | 10.78      | 2.61 | 0.59 |
| 23      | 24.00        | 2.64 | .          | .    | 3 | 24.06        | 1.12 | 24.03      | .    | 0.00 |
Values are in min. For the broken stick model, CTP = τ (Eqn. 1), and CTP = \[τ - γ - (2β₁γ/β₂)\] for the bent cable model (Eqn. 2). CI is the width (min) of the 95% confidence interval for the CTP, assuming either independent (p = 0) or autoregressive (p > 0) errors; order of the autoregressive function is given by p. The curvature of the temperature profile during transition is represented by γ. When the estimate for γ is very close to 0, the CI for CTP does not exist, and is indicated as (.). Asterisks (*) indicated series that had minor trimming of the terminal portion of the series to allow model convergence and better fit.
Fig 1. Schematic plot of bent cable (solid line) and broken stick (dashed line) regressions with identical values of $\beta_0$, $\beta_1$, $\beta_2$ and $\tau$ (see text for details). The transition point $\tau$ for the broken stick regression is the intersection of two straight lines, and is identical to the critical transition point CTP. The CTP for the bent cable regression is given by $\tau - \gamma - (2\cdot\beta_1 \cdot \gamma / \beta_2)$, but converges to $\tau$ as $\gamma$ approaches 0.

Fig. 2. Representative plots of core temperature profiles for individual rats showing the fitted bent cable (dashed black line) and broken stick (solid gray line) models overlaid on the observed data. Solid bars indicate duration of each haemorrhage increment.

A. Plot of core temperature profile for rat 11. The bent cable fit is clearly a better representation of the transition than the broken stick model; estimated $\gamma$ is non-zero.

B. Plot of core temperature profile for rat 12. Here both the bent cable and the broken stick models give identical fits; estimated $\gamma$ for the bent cable model is zero.

Fig. 3. Plot of core temperature profile, model fits, and diagnostics for rat 9.

A. Plot of core temperature profile showing the fitted bent cable (dashed black line) and broken stick (solid grey line) models overlaid on the observed data. Solid bars indicate duration of each haemorrhage increment. Although estimates of the time to transition are similar, the transition region of the bent cable fit approximates the observed data more closely than the abrupt corner of the
broken stick fit; estimated $\gamma$ is non-zero.

B. Plot of estimated residuals $\delta s$ with time obtained from the bent cable fit. The scatterplot shows a random pattern, indicating an adequate fit.

Fig. 4. Core temperature profiles for two representative subjects for which neither model could be fitted. Solid bars indicate duration of each haemorrhage increment.

A. Note relatively large amplitude ($0.5 ^\circ C$) oscillations in core temperature beginning with haemorrhage onset

B. Damped oscillation following a $1^\circ C$ reduction to new temperature set-point.
