**Title**: A Generalizable Framework for Cardiac Autonomic Dynamics: Toward Scale-Invariant Parameter Estimation in Non-Linear Models.

**Authors**: Matías Castillo-Aguilar,1,2 …, Cristian Núñez-Espinosa,1,2 \*

1 Centro Asistencial Docente y de Investigación (CADI-UMAG), Punta Arenas, Chile.

2 Escuela de Medicina, Universidad de Magallanes (UMAG), Punta Arenas, Chile

### \*Correspondence

Cristian Núñez-Espinosa, Escuela de Medicina, Universidad de Magallanes, Punta Arenas, Chile. Centro Asistencial de Docencia e Investigación CADI-UMAG, Chile. e-mail: [cristian.nunez@umag.cl](mailto:cristian.nunez@umag.cl). Address: Avenida Bulnes 01855, Box 113-D. Phone: +56 61 2201411.

## Abstract

**Objective**: […].

**Material and Methods**: […].

**Results**: […].

**Conclusion**: […].

**Keywords**: […].

# Introduction

The autonomic nervous system (ANS) orchestrates a myriad of physiological functions, with its influence on cardiac activity being particularly profound and dynamic, especially under conditions of physiological stress such as exercise. The heart, a finely tuned instrument, responds to these stressors with intricate temporal adjustments, and understanding the precise nature of these exercise-induced fluctuations in heart rhythm is not merely an academic exercise. It is fundamental to unraveling the intricate interplay between the brain and heart, a dialogue often referred to as brain-heart crosstalk, and crucially, for predicting a spectrum of health-related outcomes. This necessitates the development and application of sophisticated analytical tools capable of capturing the nuances of these physiological responses.

In the realm of modeling these complex cardiac autonomic dynamics, non-linear parametric models frequently emerge as the preferred approach. Their utility is most pronounced when there is a reasonable understanding of either the underlying data-generation process or the overall functional behavior of the system under investigation. This preference is not arbitrary; these models offer a distinctive and powerful advantage as they enable researchers to precisely characterize the influence of specific parameters that sculpt cardiac temporal dynamics during physiological stressors like exercise. This granular level of insight is invaluable. It moves beyond mere description to a deeper elucidation of the mechanisms at play, ultimately contributing to a more profound comprehension of cardiac-autonomic modulation and the intricate, often bidirectional, mechanisms underlying brain-heart crosstalk.

The application of non-linear parametric functions extends far beyond their inherent flexibility in capturing complex physiological processes. A cornerstone of their utility lies in their capacity to enable the estimation of physiologically relevant parameters. These parameters are not abstract mathematical constructs; rather, they hold significant practical value, often serving as valuable tools in health risk assessment and clinical decision-making. This interpretability stands in stark contrast to “black-box” models. While black-box models, such as certain machine learning algorithms, may exhibit remarkable predictive power, they often lack transparency regarding how their internal mechanisms generate predictions. This opacity can be a significant impediment in scientific and clinical contexts where understanding the *why* behind a prediction is as critical as the prediction itself. Non-linear parametric models, conversely, offer transparent inference. This transparency is rooted in a clear understanding of how each parameter directly influences the overall observed cardiac behavior, thereby fostering trust and facilitating the translation of research findings into practical applications.

In this context, Castillo-Aguilar et al. (2025) recently introduced a novel non-linear model. This model, cleverly constructed from coupled logistic functions, was specifically designed to capture the transient behavior of R-R intervals (RRi), the precise time elapsed between successive heartbeats, across the entire spectrum of a rest-exercise-recovery period. This work represented a significant step forward, offering a robust framework for quantifying the dynamic shifts in cardiac rhythm in response to exercise, a critical area of investigation for understanding autonomic control.

Despite their compelling advantages in terms of flexibility and interpretability, non-linear models, including the innovative one proposed by Castillo-Aguilar et al. (2025), are not without their inherent practical challenges. A primary concern is their computational intensity. The iterative optimization procedures required to estimate parameters in non-linear systems can be demanding, consuming substantial computational resources and time, especially with large datasets or complex model structures. Furthermore, a pervasive issue in non-linear modeling is the potential for identifiability problems. This occurs when multiple distinct sets of parameters can equally well explain the observed data, making it difficult or impossible to identify a unique and correct set of parameters. This ambiguity can undermine the scientific rigor and interpretability of model findings.

Various strategies have been proposed to mitigate these challenges. For instance, box-constrained algorithms based on gradient projection methods are often employed to restrict parameter exploration within physiologically plausible ranges. However, these methods, while useful for ensuring parameter sensibility, frequently fall short in adequately capturing the uncertainty associated with model parameters. Understanding parameter uncertainty is paramount for drawing robust scientific conclusions and for quantifying the reliability of model predictions. An alternative, more sophisticated approach involves the judicious use of informative Bayesian priors. These priors can guide parameter exploration within a predefined, theoretically sound space, thereby enhancing identifiability and computational efficiency. However, this approach demands a high degree of specific domain knowledge to formulate appropriate priors, which is often not feasible for highly complex non-linear models or in exploratory research settings where *a priori* knowledge is limited. Another strategy is model reparameterization, a mathematical transformation designed to ensure parameters are unconstrained over real numbers. This simplifies the geometry of the parameter space, allowing for unbounded exploration by optimization algorithms and potentially improving convergence.

A particularly significant and often overlooked challenge with non-linear models describing time-dependent trajectories, such as the Castillo-Aguilar et al. (2025) model for exercise-induced RRi changes, is the sensitivity of their parameters to the time scale of the experimental protocol. To illustrate, consider a parameter, say , with units of min-1, intended to govern the rate of exercise-related RRi decline. A value of min-1 will signify a drastically different steepness and temporal progression depending on whether the exercise protocol spans 2 hours or a mere 15 minutes. This inherent scale dependency renders the parameter uninterpretable across different experimental designs that utilize time scales other than the one (minutes) on which the model was originally validated. This limitation severely constrains the generalizability and comparative utility of such models across diverse research studies and clinical protocols. Moreover, these scale-sensitive parameters are often expressed on different magnitudes, which further complicates the already intricate processes of parameter exploration and estimation. This, in turn, translates into longer and more expensive computational times and significantly exacerbates convergence issues, including the persistent problem of non-identifiability of model parameters.

It is precisely for these compelling reasons that the current work introduces a novel scale-agnostic reparameterization of the original Castillo-Aguilar’s RRi-vs-time model. This innovative reparameterization is not merely a mathematical convenience; it offers several crucial and transformative advantages. Firstly, it will result in real-defined parameters, a characteristic that inherently leads to a computationally efficient model for parameter exploration algorithms. By transforming the parameter space into one that is unconstrained and numerically well-behaved, we facilitate faster and more reliable convergence of optimization routines. More importantly, this reparameterization will yield physiologically interpretable parameters that hold consistent significance for practitioners, clinicians, and researchers, regardless of the experimental time scale. This eliminates the aforementioned scale dependency, enabling direct comparisons of parameter values across studies employing varying exercise durations or sampling rates. Finally, building upon this enhanced framework, we will also present various derived indices that can be robustly computed from these newly defined parameters. These indices promise to provide valuable and nuanced insights into exercise-related cardiac autonomic dynamics within the broader, increasingly recognized context of brain-body crosstalk, pushing the boundaries of our understanding of physiological regulation.

# Original Castillo-Aguilar’s RRi-vs-time model

The original model, proposed by Castillo-Aguilar et al. (2025), consists of two coupled logistic functions plus an intercept. The original model, adapted to describe only the magnitude of each parameter is defined in [Equation 1](#eq-original-model).

As intended, model reparameterization, a mathematical transformation, simplifies parameter space geometry, potentially improving convergence speed and identifiability by reducing parameter correlations. Yet, its success hinges on design. Many reparameterizations focus only on numerical stability or correlation reduction, often failing to preserve or enhance physiological interpretability, particularly across different temporal scales. A reparameterization improving computation but obscuring physiological meaning has limited scientific or clinical utility, especially in interdisciplinary fields where clarity and biological relevance are paramount. The challenge lies in devising a reparameterization that simultaneously achieves numerical robustness *and* consistent physiological interpretability irrespective of experimental time scale.

In esence, we need to reparametrized the model parameters so every new parameters can extend along the real number, but provide a feasable prediction of the RRi dynamics over time. Additionally, the parameters need to be robust enought to changes in the scale of time, so the same parameters can mean the same overall shape, independent if the timescale is on minutes, hours, percentages, or time-to-event timescales.

For each parameter we present the transformation of the original parameter into the new reparameterized form, alongside the inverse transformation. In this manner, we got a new equation to plug into the original model, replacing the old parameter. In addition, the inverse transformation serves as a way to obtain the old parameters back from the reparameterized model, allowing reversibleness between model parameters.

## Baseline parameter

For the baseline parameter, we’re going to center and scale for the standard deviation () and mean RRi () observed from the RRi data. This previously computed parameters will serve to refer to the new parameter as an standardized version of .

## Exercise-induced drop parameter

For the parameter , that controls the exercise-induced drop part of the RRi curve, we’ll also scale it, so it is in the same units (standard deviations) of the parameter. This new parameter will be .

## Recovery proportion parameter

The parameter controlling the recovery proprotion is a parameter bounded at zero at the lower limit, and physiologically bounded at 1.5 or 2, with no hard upper limit. In this case, we need a transformation that allows the new model parameter to be on the real line (i.e., ). For this we limit the values of from 0 to 2, which contains physiologically extreme, but plausible, recovery proportion values.

## Rate parameters and

The parameters controlling the steepness of the exercise-induced drop and recovery are given by and parameters. These parameters are defined on the positive real line, . To convert this parameters so they can extend on the complete real numbers, we can apply a logarithmic transformation.

This also applies for the parameter.

This way we obtain real defined rate parameters and .

## Timing parameters and

These parameters control the time-dependent kinetics of the RRi curve. This means, they control the “when” things happen. To make this parameters agnostic to the time scale, we thought to make a similar implementation to the parameter, by leveraging the inverse logistic function. However, for this to make sense, we need these parameters to be constraint in the 0 to 1 range (like a probability). To accomplish this, we first need to make that (and as well as we’ll further see), are percentages of the current time range, . This can be made by declaring this new parameter, let’s say and .

For this would be:

And for it would be:

Then, we can work with this new parameter and apply the inverse logistic function to map this new parameter in the real line. This way, we obtain the new parameters and .

The transformation would to obtain from would be:

And the similar transformation would apply to obtain from :

The full operation to transform from and and back is the following:

For and the operation is simplier, given that we don’t have the term :

This sequence of operations allows to, not only estimate parameters that are computationally efficient to explore and sample from, but also, are physiologically and practically meaningful. Parameters like and are time-agnostic, which allows for the interchangeable interpretation on exercise protocols with different time-frames and protocols.

## Full reparameterized model

Considering the aforementioned transformations on the original model parameters, let’s recall the initial model structure:

By replacing the old model parameters with the new ones, we would ended up with a raw model that would look like something this:

This model can be further rewritten to rearrange the fraction in the numerator of the second logistic component like this:

Additionally, the exponents in the euler terms can still be simplified by common terms and sign propagation to arrive to an even elegant solution:

And in this way, we’ve finally arrived to the final form of the reparameterized RRi-vs-time model, which is generalizable to support a plethora of protocols and time schemes by only capturing shape-related aspects of the RRi curve, allowing its use varying experimental settings.

# Validation and empirical performance

Provide the empirical evidence that your new model indeed performs as theoretically predicted. This is where your simulation studies come into play.

## Simulation study design

Detail the setup of your simulations. What scenarios were tested (e.g., varying time scales, noise levels, parameter combinations)? How many simulations? What estimation algorithms were used?

## Performance Metrics

Clearly define the metrics used to evaluate your model (e.g., parameter recovery accuracy, bias, RMSE, computational time, specific identifiability metrics like confidence interval width or parameter correlation matrices).

## Results of Validation

Present compelling quantitative evidence (figures, tables) that your reparameterized model:

* Achieves **superior parameter recovery and reduced bias** compared to the original formulation, especially across different time scales.
* Demonstrates **enhanced parameter identifiability** (e.g., lower parameter correlations, more stable estimates).
* Shows **significant improvements in computational efficiency** (faster convergence, reduced estimation time).
* **Crucially, show that the physiological interpretation of your new parameters remains consistent regardless of the time scale of the simulated data.**

# Physiologically meaningful indices

Present the value-added aspects of your new model – the novel insights it allows.

## Derivation of indices

Mathematically derive the new physiologically meaningful indices from your reparameterized parameters. Explain the conceptual basis for each index and what specific aspects of cardiac autonomic dynamics it quantifies (e.g., total autonomic range, specific recovery speeds).

## Demonstration of interpretabilit and utility

Illustrate how these indices provide valuable, consistent, and easily interpretable insights for practitioners, clinicians, and researchers. This could involve:

* Applying them to the simulated data from Section 4 to show their consistent physiological meaning across scales.
* (Optional, if you have it and it’s concise) A brief application to a small empirical dataset to show real-world utility.
* Discuss the potential applications of these indices in health risk assessment, patient monitoring, or athletic training.

# Discussion

Synthesize your findings, contextualize them within the broader scientific landscape, and outline future directions.

* **Recap Main Contributions:** Briefly reiterate the problem solved (scale-dependency) and your primary solution (scale-agnostic reparameterization) and its validated benefits.
* **Broader Implications:** Discuss how your work significantly advances the understanding of cardiac-autonomic modulation and brain-heart crosstalk. Emphasize how consistent parameter interpretation facilitates cross-study comparisons and meta-analyses, which was previously challenging.
* **Clinical/Practical Relevance:** Highlight the translational potential for personalized medicine, biomarker discovery, and clinical decision-making.
* **Limitations:** Acknowledge any limitations of your current model (e.g., specific physiological scenarios not yet covered, specific noise models).
* **Future Directions:** Suggest avenues for future research (e.g., application to diverse populations, integration with other physiological signals, extension to dynamic exercise protocols).

# Conclusion

Provide a succinct, impactful summary of your paper’s main achievement.

Reiterate the most significant contribution (the scale-agnostic model) and its primary benefits in 1-2 powerful paragraphs.

# References

# Author Contributions

Conceptualization, MC-A, CN-E; Data curation, MC-A; Investigation, MC-A, CN-E; Methodology, MC-A, CN-E; Supervision, CN-E; Formal analysis, MC-A; Visualization, MC-A; Writing–original draft, MC-A, CN-E; Writing–review & editing, MC-A, CN-E, […]. All authors have read and agreed to the published version of the manuscript.

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# Institutional Review Board Statement

Ethical approval was obtained from the Ethics Committee of the University of […] ([code]).

# Informed Consent Statement

All participants received detailed information regarding the study objectives, procedures, and potential implications. Informed consent was obtained to ensure ethical compliance and participant autonomy.

# Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

# Conflicts of interests

The authors declare that the research was conducted without any commercial or financial relationships construed as as a potential conflict of interest.