Informing the neural network activation function with graph centrality measures: the case study of oscillating chemical reaction simulation

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Abstract. Physics provides mathematical formalisations of phenomena, such as oscillatory motion, that prove particularly useful and effective in describing characteristics of network nodes such as robustness (or conversely, vulnerability) to perturbations. At the same time, neural networks constitute tools for solving differential equations without the use of training data and without discretizing the integration domain. In particular, neural networks can prove to be efficient in calculating the numerical solution of systems of non-linear and stiff difference equations, cases in which traditional methods can be computationally cumbersome and accumulate significantly large errors. In this study, we propose a neural network activation function model that includes the vibration centrality of the physical network nodes whose dynamics we wish to simulate. We show how this can be particularly useful for the simulation of oscillating systems and analyse the case study of cellular glycolytic oscillations and the challenges that systems like that pose.

Keywords: physics-informed neural networks · activation function · oscillatory kinetics.

1 Introduction

Network modelling and simulation is a type of network analysis that, unlike analyses based on centrality indices [2,14,34], plays an increasingly important role in the process of new knowledge discovery [1]. Network analysis based on centrality measures aims at identifying the organizing principles which operate in biological systems. Network centrality indices have proven of particular effectiveness by capturing the structural attributes of a network in quantitative ways [3]. The analysis of the connectivity distribution of nodes and edges, and the motifs-based community identification have been commonly applied in various application contexts such as assessment of network robustness for pharmacology, diseases classification and, more recently, for co-morbidities studies. However, modelling and simulation of the dynamics of a network also allow the testing

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of hypotheses in a variety of application scenarios, for example in assessing the correct understanding of the mechanisms governing the dynamics itself, in evaluating the response of the network to disturbances, and in assessing possible methods for controlling and engineering the network.

Biological network analysis requires a concerted expertise from different sciences, such as physics, mathematics, computer science, biology, and chemistry, whose boundaries are becoming more and more blurred. Physics has become crucial by offering its mechanistic view of the properties and the evolution of biological systems. Namely, the application of concepts such as temperature, entropy, elastic force and resistance, to define node and edge centrality and vulnerability is providing valuable insights into both static and dynamical properties of biological systems. Beyond popular centrality measures, such as degree, betweenness and clustering coefficient, assortativity and closeness, new indices such as vibrational centrality [11,12,13] have been lately inspired by thermodynamics and statistical mechanics concepts in order to assess network vulnerability, i.e. network inertia to a stress. In fact, biological systems are highly dynamic entities that must continuously respond to environmental and genetic changes, which are independent of the organizational architecture of the network. In these cases, standard centrality indices, which entirely rely on network structural information, do not convincingly show to be able to express the network behaviour in a dynamical environment. From this standpoint, applying new physics-inspired centrality measures like *vibrational centrality*, introduced by Estrada et al. [15], is proving suitable for learning the property of network vulnerability.

In the vibrational centrality measure [13], the external stresses to which a system may be exposed are modelled through the concept of temperature. Herein temperature is meant to be a metaphor of all the different types of stress that the network can be submitted to. In line with this metaphor, nodes are rigid spheres and edges are elastic springs, submerged in a thermal bath at a given temperature [13,32]. Vibrational centrality quantifies the amplitude of the "oscillation" of a node in response to a stress.

In non-linear oscillations of a conservative system having inertia and static non-linearities[1] the amplitude is related to the inertia [36,29], which is the tendency of the node to resist a change in motion, namely its robustness. Vibrational centrality also provides information about the propagation of stimuli from a node to other nodes of the network. Indeed, vibrational centrality is composed of two terms: (i) the amount of stress adsorbed by the node, and (ii) the amount of stress reflected to the node and propagated to the other.

Recently, the increasingly prevalence of artificial intelligence techniques, and in particular deep learning, is rapidly changing the way physics contributes to the inference and analysis of biological networks. The applications of machine learning and deep learning approaches to the inference and analysis of biological networks are numerous, e.g. [6,9,17,22,27,31,37,39,25], while physics instructs the

[1] In a static non-linear systems the output depends only on the current value of the input. In other terms, a static non -linear systems is memoryless, and constitute a good approximation of for a system of chemical reactions in stochastic regime[35].

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learning of neural networks in the so-called Physics-Informed Neural Networks, which are beginning to have various applications in the life sciences [24,16,28,7].

The contribution that artificial intelligence techniques can make to the modelling and simulation of biological networks is crucial, since even small biological networks very often exhibit non-linear and stiff dynamics that invalidate the convergence and accuracy of classical methods for solving differential equations of dynamics (e.g., Finite Difference Method. Method of lines, Finite Element Method. Gradient Discretization Method. Finite Volume Method. Domain Decomposition Methods, Spectral Method, Meshfree methods - see these methods explained in [4,5,23,26], and in numerous other textbooks). A classic example of a network, which exhibits non-linear and stiff dynamics is an oscillatory network, i.e. a system of interconnected elements that exhibit periodic oscillations. This kind of dynamics is a particularly challenging case for a neural network, especially when the oscillations have a sawtooth shape, i.e. with stretches along which the derivative is almost infinite. In this paper, we show how a neural network with an appropriate sinusoidal activation function whose parameters are derived from the node vibrational centrality of the graph describing the set of chemical reactions is able to well approximate this type of oscillatory trends typical of various biological systems.

The paper is organised as follows: Section 2 presents the case study and its data, i.e. the system of chemical reaction giving rise to glycolytic oscillations. Section 3 describes the methods that were used to simulate the case study (in particular, it introduces the mathematical formalisation of the concept of vibrational centrality and the structure as well as the activation function model we propose for the neural network simulating a system of differential equations). Section 4 presents and discusses the simulations of the glycolytic oscillations obtained with a neural network. Finally, Section 5 outlines some conclusions.

2 Case study: network of endogenous oscillatory enzyme reactions

Glycolysis is the process with which living cells of nearly all organisms, including mammals, plants, and unicellular bacteria, generate energy. This process involves dividing a six-carbon glucose molecule into two three-carbon molecules known as pyruvates. Glycolysis culminates in the creation of two molecules of NADH (Nicotinamide Adenine Dinucleotide - Coenzyme 1), which play an important part in cell metabolism, as well as two molecules of ATP (Adenosine Tri-Phosphate), which is the principal energy carrier for living cells. As a result, glycolysis enables a living cell to rely primarily on glucose for energy. Interestingly, energy production in glycolysis is not necessarily a constant process; under some situations, it can exhibit oscillatory dynamics.

Glycolytic oscillations, identified almost 50 years ago, remain the prototypical example of periodic behaviour in a metabolic circuit. They last approximately 5-10 minutes in yeast when glucose is administered at a constant pace. The

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metabolic process periodically transforms the glycolytic substrate, which is given at a constant rate.

As reported by Godbeter et al. [20], glycolytic oscillations were first studied in yeast cell populations and in yeast cell extracts, and more recently they were demonstrated also in individual yeast cells, and in pancreatic β cells where they are involved in the pulsatile insulin secretion. Theoretical models [19] suggested that the mechanism of glycolytic oscillations largely relies on the reaction catalysed by phosphofructokinase (PFK). The production of oscillations by PFK can be related to its activation by one of its reaction products, adenosine diphosphate (ADP), via adenosine monophosphate (AMP).

PFK is an allosteric enzyme phosphofructokinase, which uses ATP as a phosphate donor to phosphorylate fructose-6-phosphate (F6P) in order to produce fructose-1,6-diphosphate and ADP. A model for an allosteric enzyme activated by its reaction product proposed for glycolytic oscillations can be found in [18,19]. This model is based on the concerted transition model for allosteric enzymes, to which is added the positive feedback exerted by the product [30]. To exhibit oscillations such a system must be open and in non-equilibrium conditions [20]. Therefore, in addition to PFK, the model includes the substrate input and the consumption of product in a second enzyme reaction, which may be of Michaelis-Menten type.

The reactions described in [20] are as follows. Substrate S is supplied at a constant rate and binds to the active and inactive conformations (respectively R and T) of an allosteric enzyme, resulting in product P. The latter is eliminated through a sink reaction facilitated by an enzyme with linear or Michaelis-Menten kinetics. The allosteric enzyme is made up of subunits that move between two conformational states. The product, a positive effector, only binds to the R state, causing the allosteric enzyme to change from less active to more active. See Figure 1 showing a schematic representation of the mechanism producing the oscillations.

According to [18,19] the dynamic of this system is governed by the following equations

$$\frac{d[S]}{dt} = k_1 - k_2 f([S],[P]) \tag{1}$$

$$\frac{d[P]}{dt} = r k_2 f([S],[P]) - k_3[P] \tag{2}$$

where $[S]$ and $[P]$ denote the normalized, dimensionless substrate and product concentrations, $f([S],[P])$ is the enzyme rate function which in the simple case where the substrate S binds exclusively to the most active conformation of the enzyme is given by:

$$f([S],[P]) = \frac{[S](1+[S])^{h-1}(1+[P])^h}{L+(1+[S])^h(1+[P])^h}, \tag{3}$$

Parameters k_1 and k_2 are the normalized substrate injection rate and maximum rate of the enzyme reaction, respectively; r is a normalization parameter,

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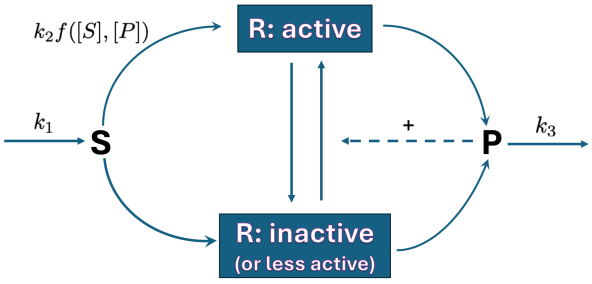

Fig. 1: Diagram of a proposed model for a product-activated allosteric enzyme reaction suggested for glycolytic oscillations as in [18,20,21]. The substrate S, introduced at a steady rate, associates with the two forms R (active) and T (less active or inactive) of an allosteric enzyme that converts it into product P. The product is subsequently eliminated in a sink reaction facilitated by an enzyme that follows linear or Michaelis–Menten kinetics.

and $L \gg 1$ is the allosteric constant of the enzyme measuring the ratio of inactive (T) to active (R) conformation in the absence of ligand. $k_3[P]$ is the product sink function, or decay term. The term $(1+[P])^h$ describes the activation of the enzyme by the reaction product P, which binds exclusively to the most active state of the enzyme. Note that $0 \leq f([S],[P]) < 1$, and $f[S],[P]) = 0$ when $[S] = 0$.

The curves obtained by numerical integration of Eqs. (1) and (2) for the following parameter values: $L = 10^6$, $k_1 = 0.5\ \mathrm{s}^{-1}$, $k_2 = 5.075\ \mathrm{s}^{-1}$, $r = 3$, $k_3 = 0.81\ \mathrm{s}^{-1}$, $h = 2$, and initial conditions $[S](t = 0) = [P](t = 0) = 0$ are shown in Figure 2.

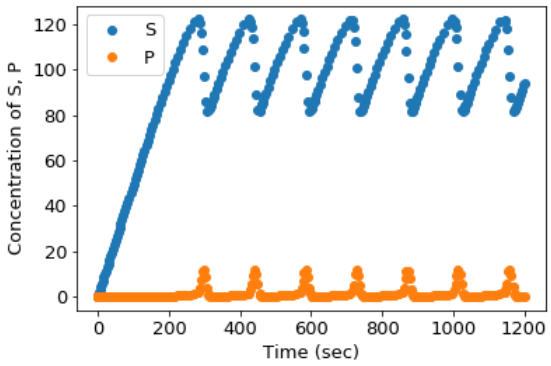

Fig. 2: Numerical solutions of Eqs. (1) and (2) obtained with explicit Runge-Kutta method of order 5(4) [10].

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3 Methods

After reporting the mathematical formalisation of the vibrational centrality proposed by Estrada et al. [15], we illustrate in this section the structure of the neural network we use to solve a system of differential equations. For the simulation of oscillatory dynamics, we propose an activation function that is a linear combination of a sinusoidal function and a hyperbolic function. The oscillation frequency - the sine argument - is deduced from the vibrational centrality of the substrate.

3.1 The network of reactions: the node vibrational centrality

Estrada et al. in [15] introduced a centrality measure, named *node vibrational centrality*. The n nodes of a network can be conceived as point in a n-dimensional Euclidean space, represented by the Moore-Penrose pseudo-inverse of graph Laplacian $L = D - A$, where D is the diagonal matrix of degrees and A is the graph adjacency matrix of the network modelled as a graph. Henceforth we denote by L^+ the pseudo-inverse of L. Each diagonal entry of L^+, denoted as l^+_{ii} for the i-th node, represents the squared distance of node i from the origin of the n-dimensional space and hence measures the node's topological centrality, which is defined by

$$C(i) = \frac{1}{l^+_{ii}}. \tag{4}$$

Lower the value of l^+_{ii}, closer the node is to the origin more topologically central the node is [33]. Two nodes connected by an arc are then represented as masses connected by springs (with elastic constant k). Furthermore, staying within the thermodynamics metaphor, a vibrational potential energy defined as

$$V(\mathbf{x}) = \frac{k}{2}\mathbf{x}^\top \mathbf{L}\mathbf{x} \tag{5}$$

is introduced, where x is the vector of node displacements. The probability distribution of node displacement is defined by the Boltzmann distribution

$$P(\mathbf{x}) = \frac{e^{-\frac{1}{T}V(\mathbf{x})}}{Z} = \frac{1}{Z}\exp\left(-\frac{k}{2T}\mathbf{x}^T\mathbf{L}\mathbf{x}\right) \tag{6}$$

where the partition function Z of the network is

$$Z \equiv \int d\mathbf{x}\exp\left(-\frac{k}{2T}\mathbf{x}^T\mathbf{L}\mathbf{x}\right).$$

Given $P(x)$, the mean displacement of the i-th node is, by definition,

$$\langle \Delta x_i \rangle \equiv \sqrt{\int x_i^2 P(\mathbf{x}) d\mathbf{x}} \tag{7}$$

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It can be shown that

$$\langle \Delta x_i \rangle = \sqrt{\frac{T}{k} l_{ii}^{+}}. \tag{8}$$

At equilibrium, the edges of the network are influenced by the parameter $\beta = 1/T$. As T approaches zero, the weights of the edges become infinitely large, causing the network to resemble a solid state of matter. On the other hand, as T increases towards infinity, the weights of the edges approach zero, resulting in a network that is devoid of edges and likened to the gaseous state. When T is equal to 1, the network is strictly structured with no loops and no multiple edges at any node, resembling the liquid state of matter.

In the model for a product-activated allosteric enzyme reaction considered i this study, we set $T = k_1$ since we consider the temperature, i.e. the thermal agitation that disrupts the nodes, is due to the substrate injection operation in the system.

We set the elastic constant of the spring corresponding to the arc connecting R with P equal to k_2. We instead set the spring constant corresponding to all the other arcs of the graph equal to 1. Since here we consider the case where the substrate S binds exclusively to the most active conformation of the enzyme, the elastic constant of the arcs from S to T and from T to P is set to zero. The adjacency matrix A and the graph Laplacian L are then as follows.

$$A = \begin{array}{c} \begin{matrix} S & T & R & P \end{matrix} \\ \begin{pmatrix} 0 & 1 & 1 & 0.000 \\ 0 & 0 & 1 & 1.000 \\ 0 & 1 & 0 & 5.075 \\ 0 & 0 & 0 & 0.000 \end{pmatrix} \end{array} \begin{matrix} S \\ T \\ R \\ P \end{matrix} \qquad L = \begin{array}{c} \begin{matrix} S & T & R & P \end{matrix} \\ \begin{pmatrix} 2 & -1 & -1 & 0 \\ 0 & 2 & -1 & -1 \\ 0 & -1 & 6 & -5 \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{array} \begin{matrix} S \\ T \\ R \\ P \end{matrix}$$

Therefore, we obtain the vibrational centralities shown in Figure 3. The substrate S is the node with the highest vibrational centrality, i.e. with the widest amplitude of oscillation (as also confirmed by the numerical solution of Eqs. (1) and (2) shown in Figure 2).

3.2 Neural network

A system of n ordinary differential equations (hereafter "ODEs") has the following form,

$$\begin{aligned} \frac{dx_1}{dt} &= F_1\left(t, x_1, x_2, \ldots, x_n\right) \\ \frac{dx_2}{dt} &= F_2\left(t, x_1, x_2, \ldots, x_n\right) \\ &\vdots \qquad\qquad \vdots \\ \frac{dx_n}{dt} &= F_n\left(t, x_1, x_2, \ldots, x_n\right) \end{aligned} \tag{9}$$

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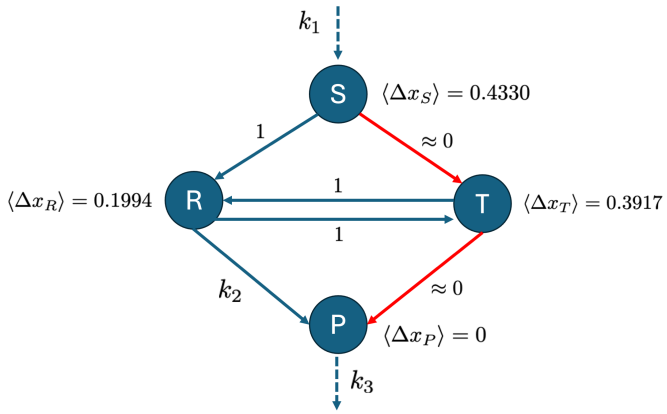

Fig. 3: Graph representing the product-activated allosteric enzyme reaction system as proposed in [20] and the vibrational centralities of its nodes.

defined on $t_0 < t < T$ with given initial values, $x_1(0) = x_1^{(0)}, x_2(0) = x_2^{(0)}, \ldots, x_n(0) = x_n^{(0)}$.

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(t, \mathbf{x}), \quad \mathbf{x}(0) = \mathbf{x}_0, \tag{10}$$

where $\mathbf{x} = [x_1, x_2, \ldots, x_n]^T$ is the $n \times 1$ matrix of unknowns (for example, the concentration of the m chemical species in time), and

$$\mathbf{f}(t, \mathbf{x}) = \begin{bmatrix} F_1(t, x_1, x_2, \ldots, x_n) \\ F_2(t, x_1, x_2, \ldots, x_n) \\ \vdots \\ F_n(t, x_1, x_2, \ldots, x_n) \end{bmatrix}$$

is the $n \times 1$ matrix of functions. The solutions of the system are the functions describing the behaviour of $x_1, x_2, \ldots, x_n$ with respect to the variable t (that, when the systems of ODEs describe the dynamics of a system of m variables usually denotes the time).

The solution $\mathbf{x}$ calculated using a neural network can be expressed as:

$$\mathbf{x}(t, \mathbf{W}) = \mathbf{x}(t, \mathbf{W}_1, \ldots, \mathbf{W}_N) = \sigma(\mathbf{W}_N \ldots \sigma(\mathbf{W}_2 \sigma(\mathbf{W}_1 t))), \tag{11}$$

and the neural network is a system of non-linear equations like

$$x(t, \mathbf{W}) = \sigma(\mathbf{W}t + \mathbf{b}), \tag{12}$$

where σ is the activation function. Through the activation function, non-linearities can be introduced into the model. The function applies to the output of the neuron and guides the network in learning non-linear complicated data patterns. Regardless of the number of layers, without non-linearity, the neural network

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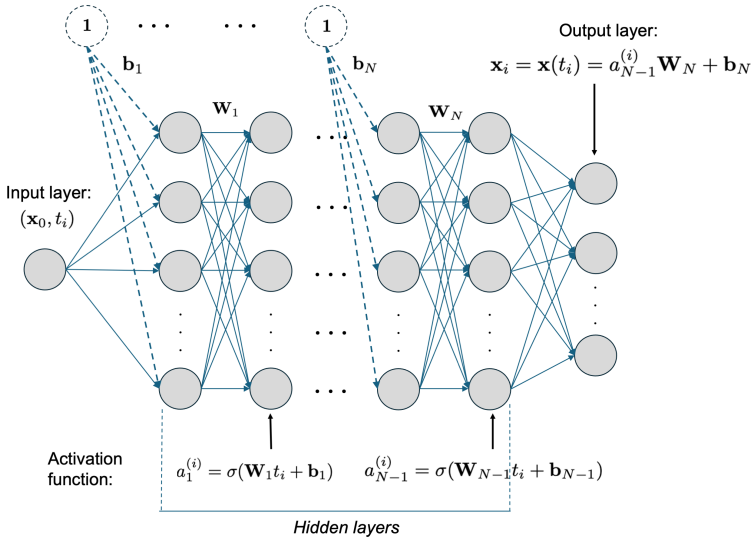

Fig. 4: Structure of the neural network for the solution of a system of ordinary differential equations. The network is fully connected and has one neuron in the input layer, and N hidden layers of p neurons each. The output layer has as many neurons as there are equations. The weight matrices $\mathbf{W}$ have dimensions as follows: $\mathbf{W}_1$ is a $p \times 1$ matrix, $\mathbf{W}_i$ (with $1 < i < N$) is a $p \times p$ matrix, and finally $\mathbf{W}_N$ is a $q \times p$ matrix, where q is the number of differential equations of the system. $\mathbf{b}_1, \ldots \mathbf{b}_N$ are the biases, $\mathbf{b}_1$ has dimensions $p \times 1$, and $\mathbf{b}_N$ has dimensions $q \times 1$.

would work as a linear regressor. Figure 4 shows a general scheme of a neural network used for the solution of systems of differential equations. Figures 5 shows that with a neural network with a sinusoidal activation function not with parameters chosen on the basis of experiments aimed at reducing the value of the loss does not approximate the numerical solution well.

We then proceed by considering the following points:

- the numerical solution shows that product fluctuations occur after the linear increase of the substrate has reached a certain value of concentration;
- the substrate is the node with the greatest vibrational centrality, i.e. the node which, when perturbed is subject to oscillations of the greatest amplitude.

To take these two points into account, we write the activation function $a(z)$ as follows

$$a(z) = a_1 \sin^2(\nu z) - \frac{a_2}{z + a_3} + a_4, \quad z \geq 0 \tag{13}$$

where z is the output of the node, $\nu = 1/\langle \Delta x_S \rangle$ (i.e. the reciprocal of the vibrational centrality of the substrate), $a_1 = a_2 = 100$, $a_3 = 0$, and $a_4 = 10$.

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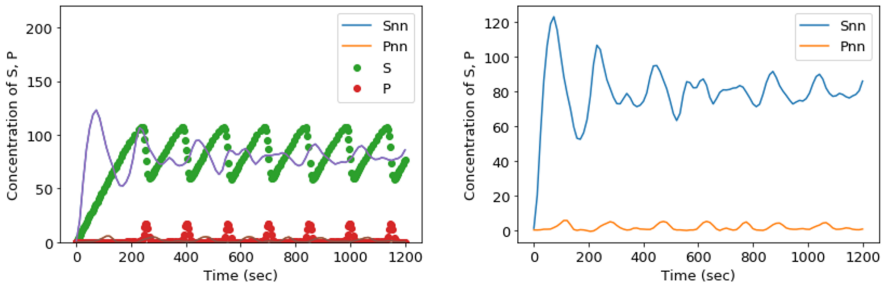
Note that although the centrality of vibration is an oscillation amplitude (hence, in general a quantity physically not dependent on the oscillation frequency), in the activation function it plays the role of an oscillation frequency. Since z is the output of the neuron, the reciprocal of the oscillation amplitude is a scaling factor of the neuron's output.

A.



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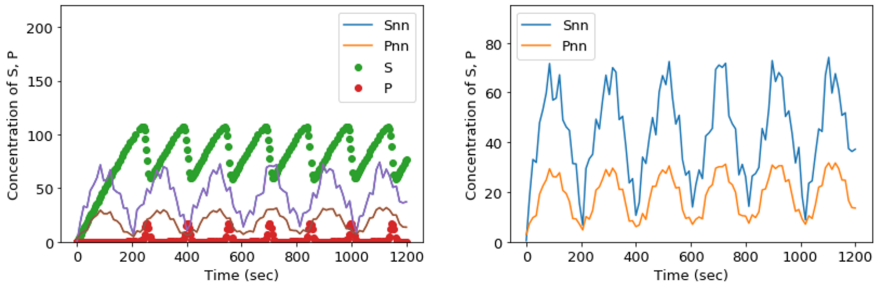

Fig. 5: Numerical solution of the system of the differential equations (1) and (2) - obtained with Explicit Runge-Kutta method of order 5(4) - compared to the output of the neural network (Snn and Pnn) with the following parameters: (A.) learning rate: 0.01, size of input layer: 1 neuron, size of layer 1: 19 neurons, size of output layer; 2 neurons, activation function $1000\sin^2(0.8x)$, and 2000 epochs; (B.) learning rate: 0.01, size of layer 1: 19, activation function $1000\sin^2(0.8x)$, and 6500 epochs. The value of the objective function at the last iteration is 42.40 (sub-figures A.), and 62.20 (sub-figures B). The agreement between the numerical solution and the neural network output is suboptimal in both cases A. and B.

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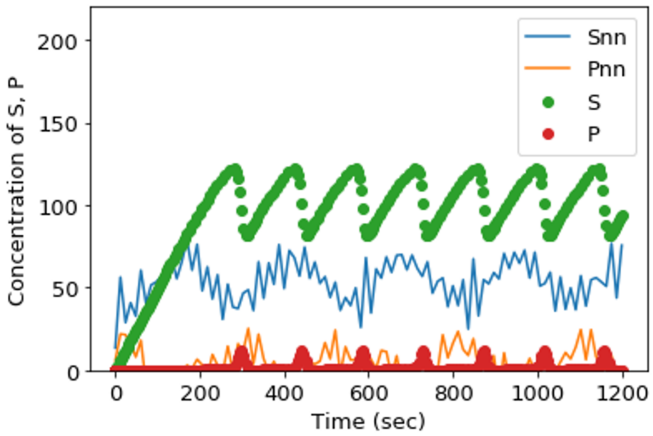

Fig. 6: Numerical solution of the system of the differential equations (1) and (2) - obtained with Explicit Runge-Kutta method of order 5(4) - compared to the output of the neural network (Snn and Pnn) with the following parameters: learning rate: 0.025, size of layer 1: 15, activation function as in Eq. (13), and 2000 epochs. The agreement between the numerical solution and the neural network output is still non-optimal, but the oscillatory behaviour is maintained over time and with the correct phase shift between product and substrate is obtained.

4 Results

The oscillatory behaviour that best approximates the one given by the numerical solution was found only in the case in which ν is equal to the reciprocal of the vibrational centrality of the substrate, i.e. $1/0.43$.

Experiments performed using values even slightly deviating from this one show a significant disagreement with the numerical solution and an incorrect phase relationship between the substrate and product curves. The correct phase relationship predicts that the product maximum immediately follow a substrate maximum. Figure 6 show the output of the neural network and the hyper-parameters are reported in the figure caption. Although the parameters found in our experiments are the only ones that reproduce the oscillatory behaviour closest to that of the numerical solution, the agreement between the numerical solution and the approximation calculated by the neural network cannot be said to be optimal. We have performed an extensive exploration of the parameter space of the activation function and the hyper-parameters of the neural network. These experiments have shown us that the reason for this disagreement is not due to improper values chosen for these parameters. The reason should rather be sought in the temporal trend of the enzyme and substrate. The analyses of Goldbeter et al. [20] show that when the enzyme responsible for product degradation approaches saturation, the oscillations take on a distinct triangle shape. When the product sink is linear, the product peak resembles a pulse.

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The decreasing sections of the impulse curve with the parameters used for this simulation have a very high slope (i.e. a derivative close to infinity) which the neural network cannot resolve appropriately.

5 Conclusions

To the best of our knowledge, we think that constructing an informed activation function with centrality measures is an innovative approach and can avoid parameter tuning through time consuming trial and error procedures. This study shows, however, that the activation function properly informed by centrality measurements and chemical kinetics data is only the first step that enables a neural network to correctly reproduce enzyme kinetics. Oscillatory trends with a sawtooth-like shape, i.e. with traits of almost infinite derivative, are the subject of further investigation. The interest of the mathematics and computer science community in studying the issue of sharp gradient is current, as the recent literature shows (for instance [8,38]). The current state-of-the art highlights the increasing urgency of using physics-informed neural networks with a robust and rigorous methodology for constructing the activation function.

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DOI: 10.1007/978-3-031-97554-7_2