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# Hierarchical Biomechanics: An Introductory Teaching Framework

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**Abstract.**

Biological organisms function as the result of a multitude of complex physical systems all interacting with one another at different length scales and over different time scales. At stages of education below university undergraduate level, this complexity often prevents the discussion of physics within a biological context, subtly implying that the two fields are completely distinct from one another. With science becoming steadily more interdisciplinary at the level of research, this distinction can therefore be quite counterproductive, and potentially even misleading for students with regard to the nature of the scientific method.

To explore the interplay between biology and physics with prospective STEM students, we present a series of formal teaching activities utilising a novel piece of experimental equipment we have designed called BioNetGrid. We are able to use BioNetGrid to cover a range of physical concepts at an introductory level, such as Hooke's law, springs in series and parallel, Poisson's ratio, elastic modulus and energy distribution. These can be presented together with specific biological systems as examples, such as biopolymer networks, enabling a discussion of the importance of biophysics in research at an earlier stage in a student's academic career.

***Keywords*** Biology, Physics, Biophysics, Biological physics, Interdisciplinary Science, BioNetGrid, Springs, Networks, Forces, Elastic Modulus, Poisson Ratio

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## 1. Introduction

The combination of both physics and biology, namely biophysics or biological physics, in educational activities at primary and secondary level is uncommon, leading to the misconception among STEM students that physics and biology (and to some extent chemistry) are separate and unrelated disciplines. In reality, to understand the behaviour of biological systems often requires specific expertise from each of the major scientific disciplines as well as high performance computing and even pure mathematics[1]. We have previously discussed this interdisciplinarity in terms of student engagement, with a focus on current research into biophysics; specifically the hierarchical biomechanics of protein-based hydrogels[2]. Our aim was to demonstrate to a student audience that such a collaborative endeavour accurately represents the current state of biophysics research in many institutions across the world. However, the conceptual combination of physics and biology is present throughout biological organisms, not just at the cutting edge of research. Indeed, examples of biological systems exist that exhibit physical behaviour akin to what students learn throughout their mandatory education period. The specific emergence of biophysics as its own discipline has been noted by educators for a relatively long time[3], and we strongly believe that introducing students to interdisciplinary ideas and examples will lead to more informed choices with regards to higher education. Furthermore, this provides an opportunity to convey the excitement and power of interdisciplinary research by making so-called 'elegant connections'[4].

To that end, we present a theoretical progression of understanding of hierarchical biomechanics. We previously reported the design and construction of a two-dimensional grid capable of supporting an arbitrary network of interconnected mechanical components under the application of external forces[2], hereafter referred to as the 'BioNetGrid'. We utilise this system to construct steadily more complex bead-spring networks, with continual reference to relevant biological examples. Our intention is that this article, together with the BioNetGrid (for which design blueprints are provided in Supplementary Information Section S1), can be used as a focus for teaching biophysics concepts in the classroom. We cover concepts such as spring constants and effective spring constants of combinations of springs, as well as elastic moduli, Poisson ratio (Supplementary Information), energy densities and others. With feedback from UK GCSE and A-level physics teachers, we have determined that a suitable audience for teaching these concepts is at the UK Key Stage 5 level of education and beyond (Ages 16+), as the exercises compliment the compulsory teaching of Hooke's law and Young's moduli in the UK A-level syllabuses[5][6]. Nevertheless, our previous experience using more qualitative interpretations of the BioNetGrid indicates that simply discussing the biological examples associated with the system can be enough to showcase the potential interdisciplinarity of STEM subjects[2].

## 2. The Challenge of Translating of Biomechanical Properties Across Multiple Length Scales

Biological systems in general have highly complex mechanical properties. From a technical perspective, the contribution of both enthalpy and entropy to the nanoscopic elastic response of even 'simple' biological systems, such as polyproteins, makes their analysis highly non-trivial.

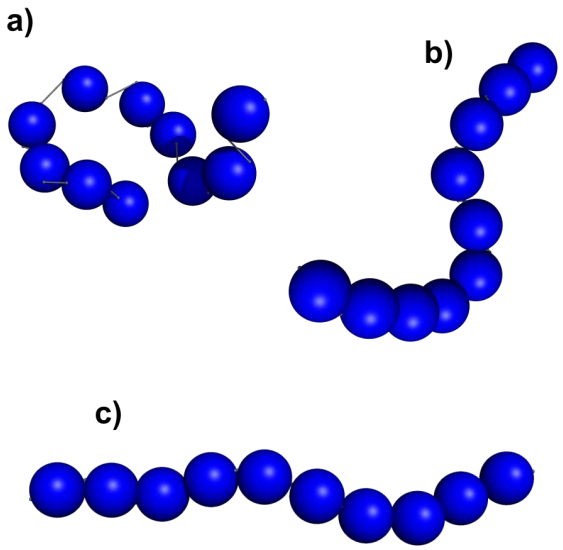



Figure 1: An example of complexity emerging from a relatively simple simulation of a biological polyprotein[7]. The average length of each amino-acid chain (spring) connecting the proteins (spheres), and the softness of the spheres themselves, determines whether their overall flexibility emerges from the enthalpic stiffness of the proteins themselves, or from their ability to entropically move past one another. a) Longer amino-acid chains result in flexible polyproteins. b) Softer spheres allow for some flexibility, even if the springs are short. c) Rigid polyproteins have very short chains and hard spheres, allowing for only a small amount of movement.

In Figure 1 we see three representative snapshots of different polyproteins which we previously modelled as spheres connected at their surfaces by Hookean springs, and simulated under the influence of temperature[7]. With respect to Figure 1**c)** as the least flexible polymer, we notice that the longer the spring component (Figure 1**a)**), the more flexible the polymer. Additionally, the softer the protein (Figure 1**b)**), the more flexible the polymer. This is because the more often the spheres interact, and the stronger that interaction is, the more of the thermal energy provided by the background temperature is absorbed by those interactions, which corresponds to an enthalpic response. On the other hand, the less often the spheres interact, and the weaker that interaction is, the more the thermal energy provided by the background temperature is used to simply move the polymer components throughout space and thus explore new polymer

configurations. This corresponds to an entropic response. It is clear, then, that even something as apparently simple as so-called 'beads on a string' is not as simple as one may initially think[8] when considering the full range of biophysical interactions. However, as will be shown in Section 4, approximations can be made such that the concepts can be described to A-level students.

To investigate this complexity in a biomechanical context, we consider biopolymer networks. These systems can be artificially designed[9], but also exist naturally within biological organisms with examples including collagen, actin, microtubule and fibrin[10]. Each of these example biopolymers has a different biological function, and they form different types of connected networks (such as ordered bundles, disordered meshes or somewhere in between) in order to meet each biological requirement. Burla *et al* provide a comprehensive review of the hierarchical organisation of these networks[10], and Broedersz *et al* outline the mechanics involved for general 'semi-flexible' polymers[9]. To introduce these ideas at a beginner level, it is sufficient to note that these entangled and interacting systems of long-chain polymers exhibit a range of interesting mechanical properties, including reversible softening under compression[11], as well as both stiffening[12] and negative normal stress under shear[13]. On the other hand, the polymers themselves can often be mathematically described by only two values: a contour length, $L_c$, which describes the equilibrium length of the polymer, and a persistence length $L_p$, which describes the stiffness of the polymer. That such a diversity of viscoelastic behaviour emerges from systems that are made of these simple nanoscale building blocks is a major point of interest in the scientific community, and a major challenge in biological and soft matter physics is to determine how mechanical properties translate across length scales[9].

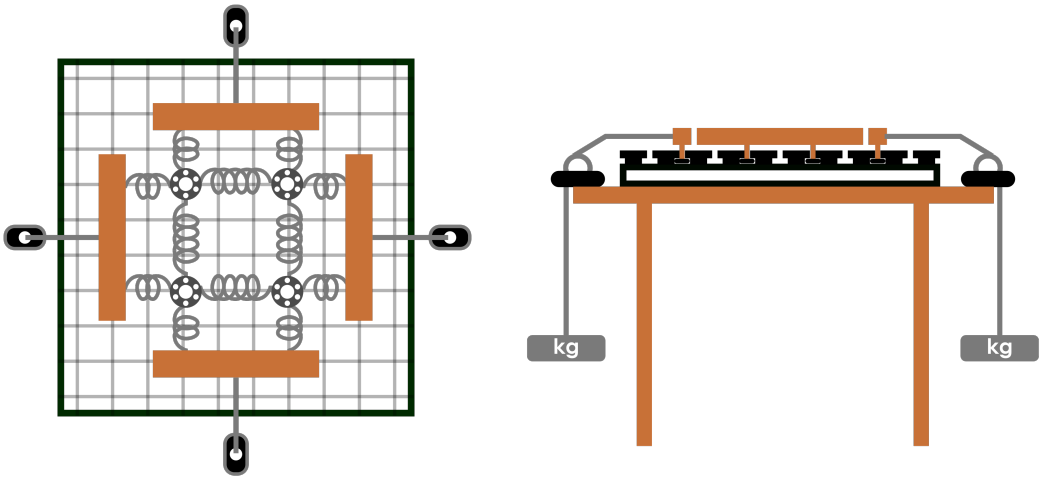
As mentioned in our previous work, of specific interest in our group are protein-based hydrogels[2]. These artificial biological systems are formed when globular proteins are made to chemically 'cross-link' with one another, forming network structures similar to biopolymer networks (see Section 4). General biopolymer networks can also form hydrogels so long as they have a sufficiently strong hydrophillic interaction with their solvent environment. In this case, the networks of biomolecules then become significantly more viscous whilst retaining their elasticity, thus becoming a gel. The combination of their biocompatibility together with their novel viscoelastic properties had led to complex biological applications for hydrogels such as tissue engineering[14, 15, 16], drug delivery[17], wound repair[18, 19] and even bioprinting with embedded cells[20]. To optimise the design of these clearly important medical innovations, it is of vital importance to understand exactly how the useful material properties hierarchically emerge from the underlying biological subunits from which they are formed.

Our group is currently using a range of experimental techniques, including atomic force microscopy and rheology, to probe the mechanics of these systems at different length scales[21, 7]. We are also interested in how the mechanical behaviour relates to the structural organisation of protein hydrogels, and are therefore using techniques such as circular dichromism, and dynamic light, neutron and x-ray scattering to probe their

multiscale structural hierarchy[22]. In this paper, however, our core aim is to share our expertise in this area to enable the general principles of biomechanics to be understood by students in the context of interdisciplinary scientific education.

## 3. An Introduction to the BioNetGrid

The schematic shown in Figure 2 has been fabricated and used in a number of engagement activities in collaboration with the University of Leeds[2]. However, there is a vast potential for more technical and in-depth discussions of biophysics using mechanical networks supported on the BioNetGrid as a focus.




(a) (b)

Figure 2: The schematic of BioNetGrid, the 2D grid designed to support arbitrarily connected bead-spring networks. The design protocol for the BioNetGrid is provided as Supplementary Information. (a) A top-down view of a network with four beads connected in a square arrangement. (b) A side view show force being applied to the network via weights and pulleys.

Figure 2a shows a simple network formed of 4 beads, shown as grey disks, connected in a square by springs and attached to the sliding network edges, which we call 'sliders', shown as brown rectangles. Figure 2b shows that force can be be applied to the network via weights and pulleys attached to each edge, inducing potentially anisotropic (different in each direction) and inhomogeneous (unequally distributed) strain to the network. Forces can also be applied parallel to each network edge, allowing us to apply shear forces to the network as opposed to the tensile forces shown in the schematic. Overall, BioNetGrid can support network structures that are as simple or complex as we require, and external forces can be applied in any of the fundamental directions commonly used in practical applications. The generality of the system enables us to discuss many of the concepts in the 'Mechanics and Materials' topic within the UK AQA syllabus[5], and

the 'Materials' topic in UK Edexcel syllabus[6], in such a way that the hierarchy of the concepts is made clear. For example, we can discuss how an effective spring constant, or Young's modulus, of a full network of springs relates to the spring constants of the individual springs. But we can also go beyond the syllabus, such as by adding weights or springs in multiple directions to discuss Poisson's ratio and bulk modulus. This generality is useful to us as biophysicists in that many of the systems we can build on the BioNetGrid will also have some biological analogue.

## 4. Exploring the Mechanical Diversity of Biological Systems Using BioNetGrid

While A-Level physics students begin to consider the mechanical properties of macroscopic objects such as springs, there are interesting parallels to be made in biological systems. For example, single alpha helices (SAH) can be found acting as a bridge between functional domains in $\sim 4\%$ of proteins[23], including the molecular motor myosin[24]. Due to their helical shape, these important biological motifs are known to act as 'constant force springs'[25]. Whilst not exactly the same as a Hookean spring, this characterisation still suggests that the SAH domain fulfills a similar role as a macroscopic spring would in the mechanically dynamic environment of the cell; enabling energy to be absorbed into the spring rather than lost to the environment.

Many springs connected in series with intermediate beads can be used as a representation of almost any polyprotein[7] but here we specifically refer to titin[26]. The giant elastic protein titin functions as a molecular spring and is responsible for passive elasticity in human cardiac muscle. The mechanical properties of titin, including the effective spring constant, can be tuned to match the changing mechanical demands placed on muscle[27].

Connected in parallel, we may think of an array of biopolymers, such as the protofilaments which form a microtubule[28]. Protofilaments themselves are formed of a subunit called tubulin, as so we may consider a microtubule as an ordered network of beads and springs in parallel with one another. Finally, we could represent protein networks and hydrogels as discussed in more detail in our previous work[2]. In general, any network of elastic objects can be modelled to some extent using a set of connected beads and springs, and so we may go as far as to represent individual protein molecules on the grid, where the beads represent atoms, stiff springs represent covalent bonds and weaker springs represent other interactions such as electrostatics. Realistically, though, the vast scope and complexity of biology means that there are countless relevant examples. We provide the following citation as a guide[29], but leave it up to the individual reader to decide what their students would find interesting.

The following sections move through a logical hierarchy of various biomechanical concepts using the BioNetGrid equipment. These concepts ought to be accessible to A-level physics students, given the current A-level syllabuses, but when presented on the BioNetGrid they may be intuitively understood by A-level biology students as well.

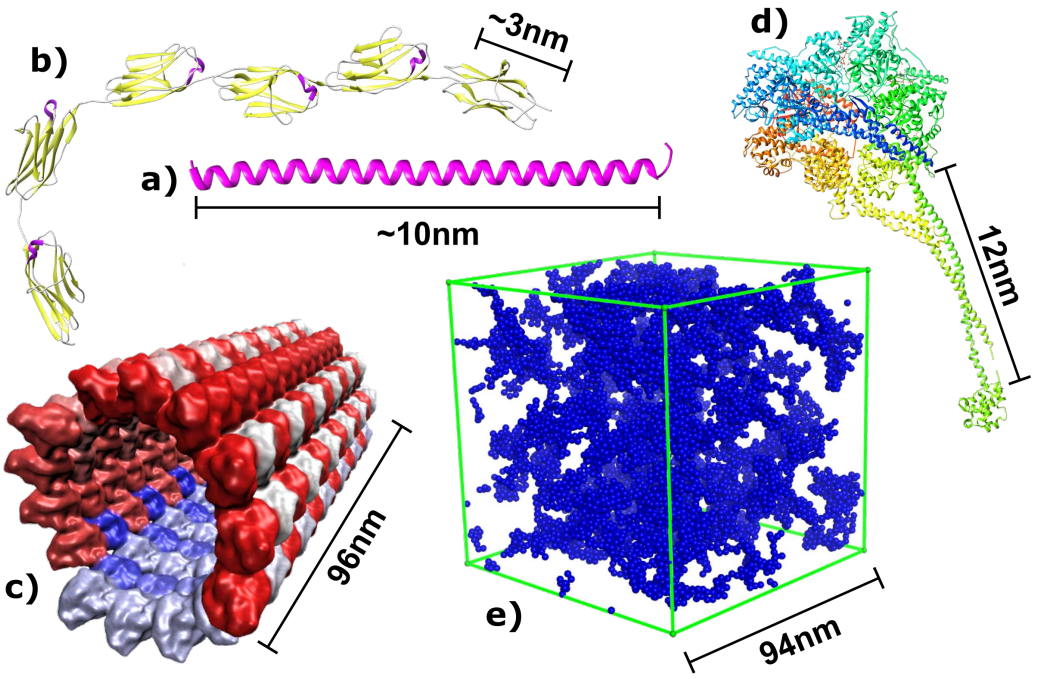



Figure 3: Representations of the biological examples we refer to throughout this work. (a) A single $\alpha$-helix (SAH) domain from the molecular motor myosin-VI[32] (b) A series of Ig subdomains of the titin molecule[33] (c) A 96 nm segment of a microtubule, assembled from 84 $\alpha\beta$ tubulin dimers[34] in accordance with the results of Imai *et al* [35]. A protofilament is highlighted longitudinally in red. (d) A monomer of the molecular motor dynein[36]. (e) A simulated protein hydrogel structure formed of spherical 'proteins' with radius $R = 1$nm.

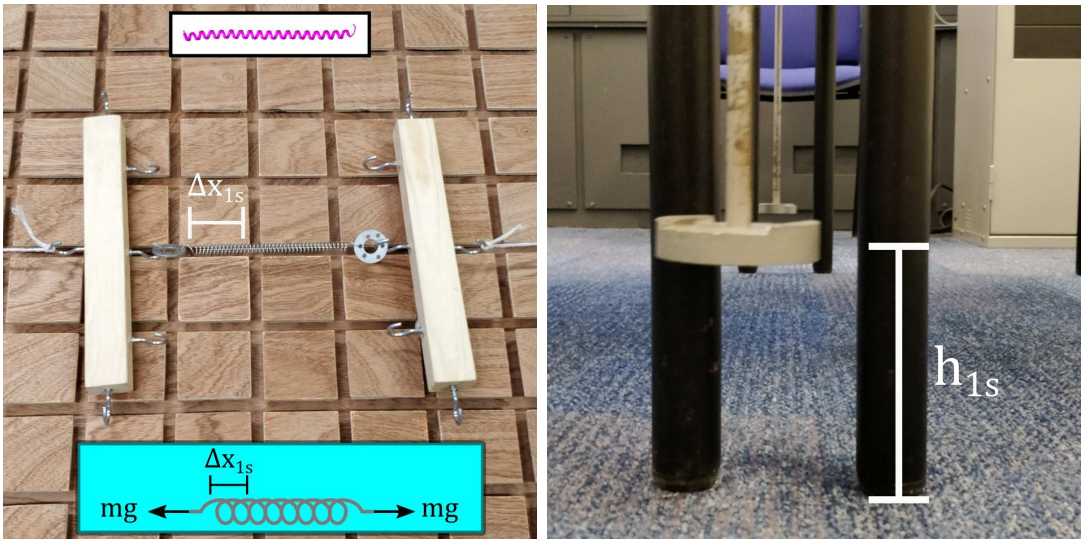
Additionally, the biological examples we present (shown in Figure 3) may be recognised by A-level biology students, but when represented on the BioNetGrid these aspects of biology can be explained to A-level physics students[30, 31].

### *4.1. Springs and Spring Constants*

We begin by attaching a single spring with spring constant $k$ to opposite sliders and adding one unit of weight, $m$, on each side to impose tension in the spring but zero net force overall. This setup is shown in Figure 4. Assuming the grid has been sufficiently lubricated to ensure negligible friction on the grid itself, Hooke's law provides our force-balance equation for this system

$$\Delta x_{1s} = \frac{m}{k} g, \tag{1}$$

where $\Delta x_{1s}$ is the extension in the spring and $g = 9.81\text{m/s}^2$ is gravitational acceleration on Earth. This will result in the weights themselves being above the floor at a height we will call $h_{1s}$, as shown in Figure 4b. From the geometry, it can be shown that for




(a) (b)

Figure 4: A network formed from a single spring connecting two opposite sides. (a) The network structure and associated mechanical diagram, with the represented biological system (SAH domain) shown at the top. (b) The resulting height of the attached weights.

any $\Delta x$ we measure in a single direction

$$h = h_0 - \frac{1}{2}\Delta x, \tag{2}$$

where $h$ is the height of the weight platform above the ground, and $h_0$ is the height from a single spring and in the complete absence of weight. Therefore, for our specific example

$$h_{1s} = h_0 - \frac{1}{2}\Delta x_{1s}. \tag{3}$$

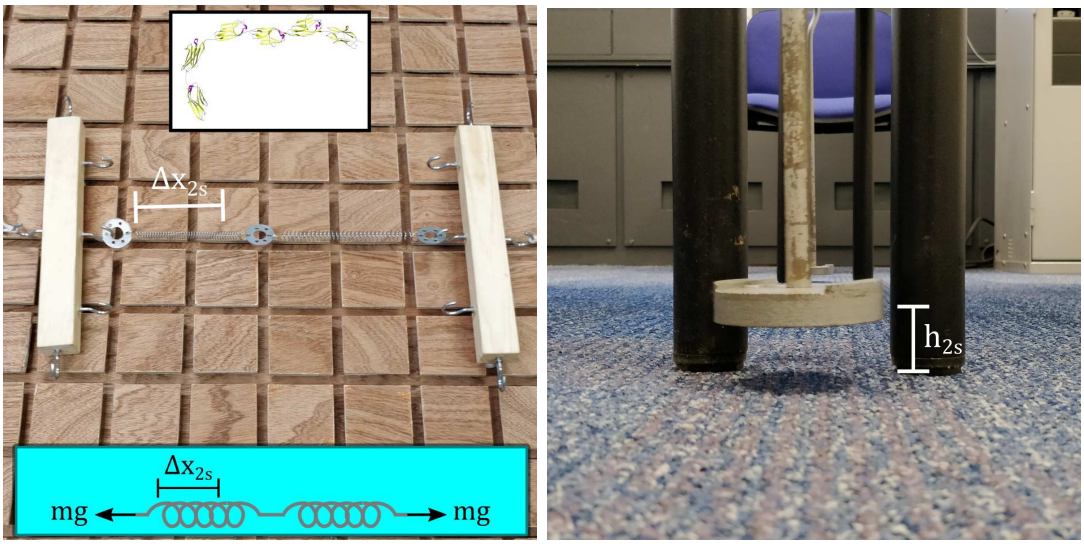
As $\Delta x_{1s}$, the spring extension, increases, Equation 3 shows that the height above ground will decrease as expected.

With reference to Figure 3, a single spring can be thought of as representing a SAH domain. Further, the application of external force in this manner is approximately equivalent to a force spectroscopy experiment performed using atomic force microscopy (AFM)[37]. With AFM, we control the force we are applying to the system and measure the associated extension, and we can calculate the spring constant of a biological structure like a SAH domain[25]. Very generally speaking, biological molecules have spring constants on the order of 1pN/nm - 10pN/nm, or, 0.001N/m - 0.01N/m, which can be directly compared to the values calculated using BioNetGrid.

### *4.2. Multiple Springs and Effective Spring Constants*

#### *4.2.1. Springs in Series*

Figure 5a increases in complexity from Figure 4a in that we have two springs connected in series, both with the same spring constant, $k$. For multiple springs in




(a) (b)

Figure 5: A network formed from two springs connecting two opposite sides. The two springs are simply connected in series. (a) The network structure and associated mechanical diagram, with the represented biological system shown (titin polyprotein) at the top. (b) The resulting height of the attached weights.

series, the effective spring constant representing the stiffness of the whole system, $k_{eff}$, can be found as follows

$$\frac{1}{k_{eff}} = \sum_i \frac{1}{k_i} \tag{4}$$

In other words, we sum the inverses of the individual springs. As such, for our new system we find $k_{eff} = k/2$, leading to a new equilibrium equation

$$\Delta x_{2s} = 2\frac{m}{k}g. \tag{5}$$

In Figure 5a, we have shown the extension only over one of the springs for simplicity, whereas in fact it would be spread equally between both springs as a consequence of the overall energy of the system being minimised. Nevertheless, as the extension $\Delta x_{2s} > \Delta x_{1s}$, we would expect the height above the floor $h_{2s} < h_{1s}$. Substitution of Equations 1 and 5 into Equation 2 shows this more formally

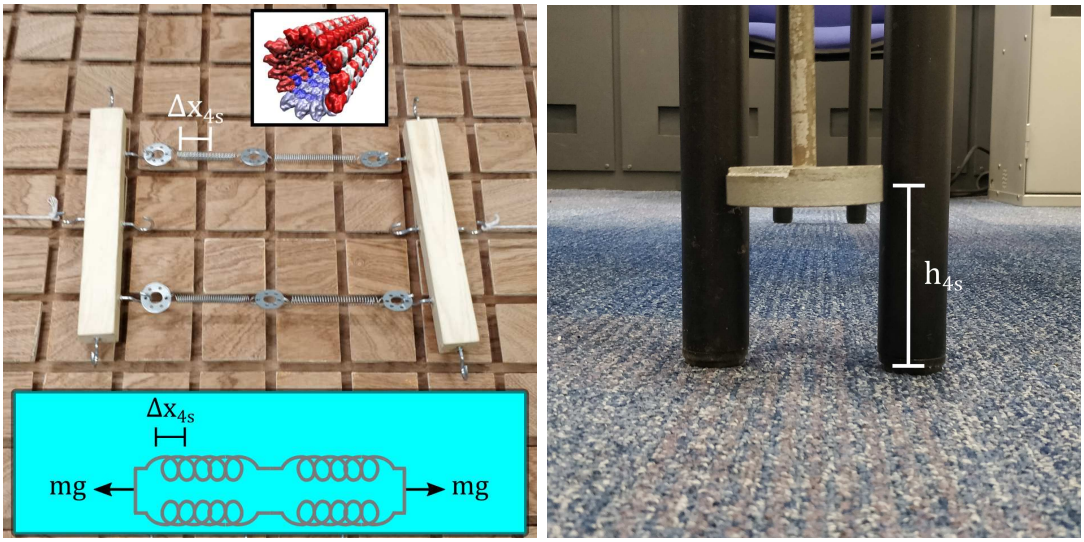
$$h_{2s} = h_{1s} - \frac{1}{2}\Delta x_{1s}, \tag{6}$$

and indeed, this is what we see in practise in Figure 5b. With reference to Figure 3, two (or more) springs connected in series may be thought of as representing different protein domains. Specifically, with the disks being significantly more rigid than the springs, the assembly above could represent the titin polyprotein as detailed by Linke, who also used AFM to study both the elastic and plastic behaviours of the system[38]. The rigid disks

and more flexible springs may respectively represent mechanically distinct subdomains of titin[39], showing how its overall flexibility and response to external forces can be modulated in different ways by altering each biological 'component'.

### *4.2.2. Springs in Parallel*

We can now show that the addition of springs in parallel has the opposite effect to adding springs in series. We include an additional set of two series-connected springs into the network as shown in Figure 6a.




(a) (b)

Figure 6: A network formed from four springs connecting two opposite sides. Two sets of two series-connected springs are connected in parallel. (a) The network structure and associated mechanical diagram, with the represented biological system (microtubule) shown at the top. (b) The resulting height of the attached weights.

As the two sets of series-connected springs are themselves in parallel with one another, the effective spring constants simply sum together as normal. The result is that the effective total spring constant, $k_{eff}$, for this final network is equivalent to a single spring, and thus we would expect $\Delta x_{4s} = \Delta x_{1s}$ and $h_{4s} = h_{1s}$. This is approximately what we observe in Figure 6b.

An important point to emphasise here is that although the effective spring constant is the same in Figures 4 and 6, because the total weight applied to the system is the same, it follows that the amount of energy stored in each spring in Figure 6 is a factor of four less than in that in Figure 4. The total energy from the weights is able to spread throughout all of the available network. Manually interacting with the springs in each network shows that the individual springs in the four spring system are much less strained than the single spring in the one spring system. Together, these observations indicate that the energy *density*, in addition to the total energy, is an important property

in these connected networks systems. In principle, this means that the four spring system could withstand a much larger amount of weight than the one spring system before the springs began to plastically deform or even snap. The energy per spring (energy density) is less in the four spring system, and so each spring has less energy to accommodate, which could be confirmed with the inclusion of a Newton meter. In essence, the four spring system has an increased ductility with respect to the one spring system.

With reference to Figure 3, we may begin to imagine more complicated arrangements of beads and springs as representing protein networks and hydrogels. However, this network is currently quite well-ordered, and so instead we may imagine them as beginning to represent a microtubule. Microtubules polymerise in two-dimensions, eventually forming large, hollow tube[28], and so the continual addition of beads and springs both in series and parallel on the BioNetGrid would lead to such a structure. Given its shape, we might imagine that the microtubule itself has associated elastic properties. Indeed, the Young's modulus (detailed below) of a stabilised microtubule has been measured to be approximately 4.6GPa[40], which an earlier work described as 'similar to Plexiglass'[41][42]. This is much stiffer than the earlier SAH domains, and thus we observe that the range of mechanical behaviours throughout biology is vast.

## 5. Discussion and Conclusions

We have described a hierarchical development of understanding of bead-spring networks using BioNetGrid up to the complexity of pre-university physics course content, with continuous reference to appropriate biological systems. Methods to explore additional, more complex biophysical concepts such as Young's modulus, Poisson ratio and Bulk Modulus together with associated biological examples are provided in Supplementary Information Section S2.

To determine the usefulness of the BioNetGrid in conveying these biomechanical concepts, the materials and approach were shared at an Institute of Physics (IOP) 'Continuing Professional Development (CPD)' event for physics teachers in the United Kingdom. This was an important opportunity to gain feedback on the clarity of the teaching concepts, its applicability to physics students and the current education syllabus, and its practicality for supporting student learning in the classroom. Feedback was in the form of discussions with practising teachers, teachers currently completing their training and leaders of teacher training. There was a consensus amongst all groups that the biomechanical concepts covered in Section 4, was a suitable level for UK A-level (i.e. pre-university) physics students. The most obvious connection being with the 'Materials' sections of the different A-level syllabuses and the areas concerning Hooke's law, Young's moduli and springs in series and parallel. Teachers highlighted that the more complex examples (Supplementary Information Section S2) would serve as useful high level problem-solving challenges for students, providing opportunities to expand to more advanced concepts in mathematics as well as physics.

An interesting outcome of our engagement with teachers was the feedback that more support would be welcomed in communicating the usefulness of physics in terms of future career prospects to students and their parents. While both the students and parents were observed to be familiar with physics as a route to teaching, awareness of alternate career routes was more elusive. Teachers therefore welcomed the opportunity to introduce physics coupled with biology, and which connected traditional topics such as springs and forces with applied topics such as biomaterials and healthcare. Teachers advised that UK Year 12 (ages 16-17) was a suitable age to introduce interdisciplinary concepts to students considering a route in STEM, as it is at this age that students are encouraged to think about their career trajectories and higher education choices.

A report by the British Academy in 2016 explicitly identifies the essential role of interdisciplinary research in addressing the complex problems and research questions posed by global social, economic, ecological and political challenges[43]. Almost in parallel, a review into the UK Research Excellence Framework (REF) noted an under-representation of interdisciplinary research, and suggested that interdisciplinary research will, if anything, become more important by the time of the next REF review in 2021. These observations have since borne fruit and, together with the British Academy, the Royal Academy of Engineering and the Leverhulme Trust, the Royal Society have created the APEX awards, which grant research funding explicitly to interdisciplinary research ventures[44]. Introducing the critical interplay between physics and biology in the interdisciplinary research environments and with respect to modern day scientific discoveries is therefore key information to communicate to students before they make their university education choices.

Overall, and with reference to our original paper[2], we have found that interdisciplinary biophysics concepts are welcomed in both an outreach and teaching capacity. For outreach and at less formal events, a general discussion and introduction of different biological systems is sufficient to engage an audience, especially if they have never considered the relationship between biology and physics before. We have also seen here that a more robust theoretical progression can be performed using the BioNetGrid, with reference to specific biological systems, and indeed, the current research and experimental techniques we used in the lab to investigate biophysical systems. We hope that this breadth of engagement will help students (and the general public) see the equivalent breadth and overlap of the different scientific disciplines, allowing them to make more informed decisions about their education and future careers.

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