FILAMENT NETWORKS USING THEORETICAL PHYSICS

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About the author

Kristian Müller-Nedebock's association with Stellenbosch began when his parents moved the family here from his place of birth, Eshowe, in KwaZulu-Natal. With predilections for libraries, Lego and Latin, his pursuit of drama, music and experimental construction and electronics projects at home pointed toward a future academic career. Eventually, after enthusing about many disciplines, conversations with inspirational academics at Stellenbosch University led Kristian to settle on the study of physics.

Following his B.Sc. and honours degrees, with a focus on theoretical physics, Kristian received a scholarship from the Emanuel Bradlow Foundation to pursue Ph.D. studies as a member of St John's College, Cambridge. It was at the University of Cambridge, under the supervision of Professor Sir Sam Edwards at the Cavendish Laboratory, that he commenced studying aspects of the networks that are also the topic of this inaugural lecture. But he also attended many superb concerts played on period instruments, punted on the Cam and discovered that May Week occurs in June.

Kristian subsequently moved to Mainz, Germany, as a post-doctoral researcher. There he derived equations for the behaviours of various types of polyelectrolytes and polyampholytes – electrically charged polymers. (It is perhaps also there that his accent became completely untraceable for most listeners.) During this period an unexpected encounter in Paris eventually led to the sequence of events that culminated with his appointment in the Physics Department at Stellenbosch University.

Kristian spends his time tracing and assembling the mathematical-physical threads for filaments as they are found in cells. His theatre is the lecture hall.

He has taught at the African Institute for Mathematical Sciences. He is currently serving on the council of the South African Institute of Physics, which also awarded him the Silver Jubilee Medal in 2003. Every so often he still uses a smidgeon of Latin.

1   The role of statistical physics

Physics is the empirical science that investigates matter and its properties in space and time, and, indeed, the features of the very space and time with which matter is associated. Accordingly, physicists' attempts at understanding the physical world range in perspective from the universe itself to particles on the tiniest conceivable length scale, and span the time from the Big Bang thirteen billion years ago to the short durations of quantum mechanical transitions measuring only quadrillionths of a second. In order to be able to formulate scientific statements, experimental methods are utilised to make measurements and these numbers need to be compared constantly with the paradigms of our theories. As our knowledge of the physical world becomes more refined, the theoretical foundations, the experiments and the nature of the quantities that we need to measure change too.

One primary endeavour of physics is to identify and determine the properties of the most elementary constituents of matter. The search for elementary particles associated with theories of matter continues and has received much public attention through the successful major discoveries in large international experiments at the Large Hadron Collider. However, we also know that huge numbers of elementary particles acting together produce a wealth of interesting and frequently confounding collective phenomena – that having identified fundamental particles and forces there is still much to understand about how these produce everyday physical phenomena. Determining the elementary constituents of a physical system does not necessarily imply that the system of which they are a part is yet completely understood.

Statistical physics is one of the branches of physics that explores ways of connecting the properties of matter on some elementary scale, denoted as *microscopic*, to a larger *macroscopic* scale where large numbers of these microscopic elements interact.[1] An example of a common statistical physical question is the following: How do we take our knowledge of some species of molecules and the mutual forces between such molecules to describe the fact that these molecules can condense from a gas to a liquid and eventually form a solid? Statistical physics also mediates between the different quantities one should measure at different scales. For instance, for a single microscopic gas molecule it is probably useful to know the speeds or energies of the particles, but for a truly large group of particles the temperature or pressure are far better characterising quantities.

Since physics knowledge of any experimental system of many particles is always incomplete, it is certainly true that only a limited degree of microscopic details may be available while there are also limitations on certain macroscopic measurements for any given system. Therefore it is sensible to ask whether certain macroscopic properties might be compatible with a hypothetical microscopic scenario. The strategy is that, using this *modelling* approach, one might learn about possible microscopic explanations for a certain type of macroscopic behaviour.

The role of theoretical physicists is to engage with these models, to cast them in the appropriate mathematical formalism and to deduce the physical phenomena and predictions that are encoded within the framework. Should a model not produce predictions that are compatible with experimental observations, careful consideration is required whether it should either be refined or discarded, unless, of course, there are good reasons to doubt the experiment.

A typical formalism of a statistical physical model contains the mathematical description of the states of particles that constitute the system; the laws of physics for these states change as the particles are influenced by each other and by their environment. As in human experience, it is the interactions that make everything interesting, but also rather complicated and challenging. The algebraic descriptions developed in theoretical physics do not only represent formulae to use in computing the quantitative results of experiments but, more fundamentally, they express the logical and physical relationships between various quantities. Mathematics provides a compact and precise language with which to explore the connections between physical quantities, to weave together related strand of arguments that should lead to the discovery of novel contexts and interpretations.

In this inaugural article the focus will be on systems of intermediate size, where polymer molecules or filaments assembled from molecules will form the important basic constituents, and the macroscopic scale ranges from nanometres to centimetres. Networks are formed when the molecules or filaments become linked to each other by permanent, reversibly attaching or moving linking units. The resultant system can now transfer forces across the whole network rather than the single macromolecules. Its macroscopic properties are due to the combination of the properties of the chains, the linking units and the nature of the network. Networks not only lie at the foundations of the classical theory of rubber elasticity, but also occur in cells as various parts of the cytoskeleton. Here there is much scope for new and fascinating statistical physical modelling.

Recent progress in experimental techniques has made possible astonishing insights on the physics of the cell and subcellular structures. Fluorescent labelling together with super-resolution microscopy enableFigure,

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[1]This number of particles is enormous; it is expressed in terms of Avogadro's number that is of the order of 100 000 000 000 000 000 000 000.

for example, the tracking of the shape and fluctuations of filaments of the cytoskeleton in real time. Optical tweezers can be used to manipulate individual strands of DNA to tie knots in these strands. One can also determine the tiny forces exerted by filaments or molecular motors. Such new observations require novel biophysical models and theoretical physical approaches. Clearly, it is also an exciting time for both cell biology and physics, since particular physics questions are truly relevant to the functioning of biological systems. Furthermore, the experimental tools currently available and those that will still be developed will prove to create an excellent symbiosis of physics with biology, physics experiment and theoretical modelling.

2 Networks of filaments

In their simplest forms networks simply consist of microscopic filaments or polymer chains that are tied together. In Figure 1 a so-called cross-link is depicted as joining two filaments. The cross-link might attach the two filaments to one another either permanently or temporarily. Extrapolating the single link to large numbers of cross-links for many different chains yields a three-dimensionally connected structure of linear molecules. With a sufficiently high density of permanent linkages and polymer chains the network is able to bear loads and deform in response to applied forces, which is not a property the individual unconnected chains would have shown.
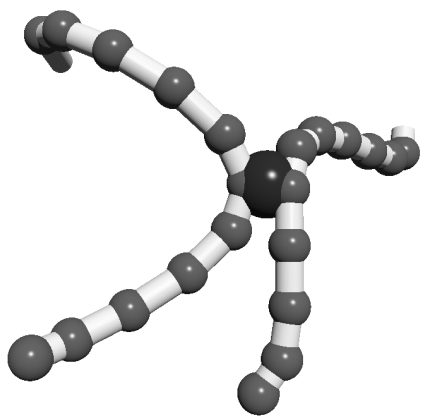

Figure 1: Two filaments that are cross-linked.

Various modes of linking filaments or chains into networks occur besides cross-linking. The ends of chains can be combined into groups and thus influence the *functionality* of the junction, which is given by the number of parts of strands emerging from a particular junction. The networks may contain contain many closed loops of polymer chains or may be completely without loops

in a tree-like structure. The reader can imagine that the way in which the networks are connected influences their elastic properties fundamentally.

2.1 The components

As already discussed, the minimal components of the network are the polymers or filaments and the linkers of these chains. Polymers, of which the double helix depicted in the cartoon of Figure 2 is an example, have intrinsic mechanical properties and interactions with each other and their fluid environment. The stiffness of filaments is significant. It is expressed in terms of the *persistence length* over which the chain remains more-or-less straight in its thermal environment.

In cells actin filaments (Figure 3) and microtubules (Figure 4) both play important structural and other biological roles and form part of the cytoskeleton (Fletcher and Mullins, 2010). The persistence lengths of these filaments are greater than for many synthetic polymers for which polymer network theories have been developed. The filaments themselves can polymerise or depolymerise and can be cross-linked in an astonishingly varied number of ways. Actin filaments can form tree-like structures by the branching effects of the Arp2/3 complex (Rotty et al., 2012). In erythrocytes a network is formed of spectrin whose filaments link into a network by mutual entwinement.
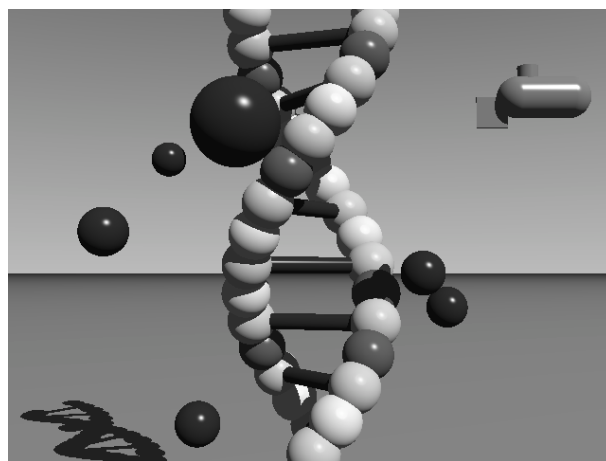

Figure 2: A schematic illustration of a double-stranded molecule, depicted here with counter-ions that affect its electrostatic interaction. (The water molecules are not shown, but indicated by the rather unrealistic submarine.)

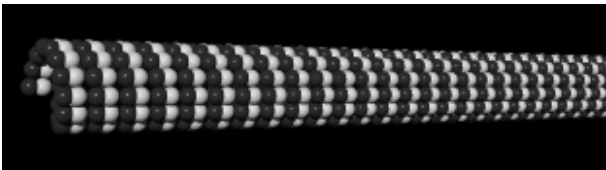Figure 3: The actin filament consists of a simple arrangement of dimers.

Figure 4: Microtubules are stiff polar filaments.

2.2 The thermal environment

The filaments typically are not isolated but move around in a surrounding fluid that is characterised by a temperature. A thermodynamic system at a given temperature above absolute zero will always possess kinetic energy (i.e. its molecules will be in a state of motion or vibration) and the hotter the system becomes the more vigorous this motion becomes. Consequently the molecules of the fluid surrounding a polymer as depicted in Figure 5 will exert forces on the chain and constantly rearrange its conformation. Thinking of the chain as analogous to a rope being held by two persons that is being wiggled along its length (the wiggling motion being the thermal effect), one can intuitively understand the forces of contraction that the rope exerts on the two people holding it.

The statistical physical equivalent of the conclusion above for the mathematically simplest model of a polymer chain can be formulated in terms of a measure related to the number of possible chain conformations that are compatible with a certain separation of the ends. This measure is known as the entropy S which decreases as the chain is ever more tightly stretched. A fundamental thermodynamic law states that systems seek to maximise their entropy. Upon brief consideration, it is clear that this statement is compatible with the attractive force of polymer ends. For a stiff polymer, where bending also costs energy, it is the Helmholtz free energy that must be minimised:

$$F = E - TS. \tag{1}$$

The equation means that the statistical physical system will tend to minimise its energy E and simultaneously maximise its entropy S, and how the systems balances these depends on the temperature T.

For a polymer network in *equilibrium*, Equation (1) encodes the statistical physics of the properties one wishes to understand. However, the individual quantities in that seemingly simple mathematical expression are extremely difficult to calculate. One of the reasons for this is that the permissible configurations of a whole network of molecules are extremely complicated. Since the polymer chains are now connected, the conformation of one chain is no longer necessarily independent of the conformation of any other chain, as the chains are well connected.
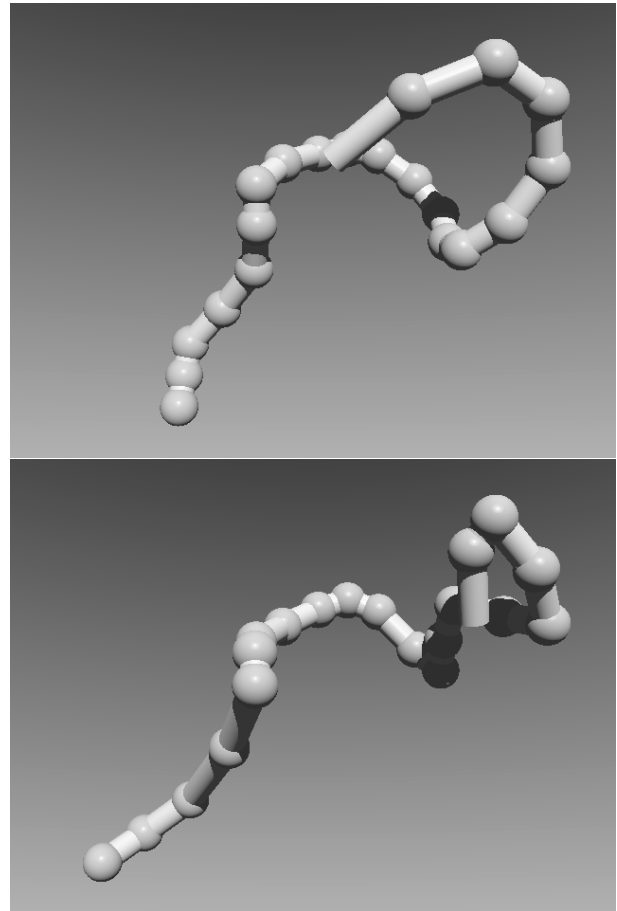

Figure 5: Two different conformations of a polymer chain.

2.3 Measuring the response and structure

Notwithstanding the challenges of calculating the quantities in Equation (1), if it is possible (and it is) to compute good estimates for these quantities, a researcher is in the position to derive the mechanical properties of the network to be modelled. One thinks of the network being localised in some containing box. The question then arises how the Helmholtz free energy would change if the box were somehow stretched or deformed with

the network inside. The *response* of the system would reveal the elastic properties.
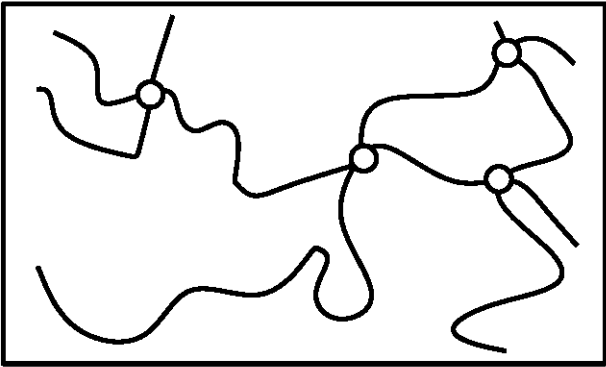

Figure 6: A cross-linked network.

3 Equilibrium networks

For the computation of the free energy one usually considers the system to be in a state of equilibrium, which means that the average behaviour of the system does not change over time and that no constant addition of energy is required to maintain the system in this constant state.

3.1 Counting all connections: disorder

A question that arises is *which* realisation of a network one should choose in order to calculate its properties. This rings especially true in that hardly any microscopic system can be controlled well enough to be able to specify or characterise which polymer chain is linked with which other chains at what part of their lengths. A network that could be prepared repeatedly from the same number of original chains and cross-links would in all likelihood have a completely different connectivity each time it is cross-linked as this would depend on the instantaneous conformations of the chains and cross-links at the moment of cross-linking.

Indeed, a statistical physical treatment needs to include the *randomness* or *disorder* that is inherent in the cross-linking process. Moreover, one should expect that the disorder, although significant on the microscopic view of the system, has little effect on the overall macroscopic quantities determined using statistical physics methods. In a seminal work, Deam and Edwards (Deam and Edwards, 1976) addressed the role of disorder and introduced a method with which one is able to perform the average over all possible cross-links. Later Solf and Vilgis (Solf and Vilgis, 1995) also showed under certain circumstances that macroscopic properties are independent of the microscopic cross-link disorder.

3.2 Enforcing the links

The statistical physical sum that leads to the free energy needs to enumerate all possible conformations of the chains in the network subject to the permanent cross-links keeping the same parts of the chains co-localised. Only after the macroscopic free energy (for example) has been calculated may one average over the different compatible versions of the disorder. The distinction of these two averaging procedures is crucial when dealing with permanently linked networks.

The networking constraints require the descriptions of the polymer chain as a series of coordinates for the N chemical bonds of one polymer chains

$$\left\{ \boldsymbol{r}_1^{(1)}, \boldsymbol{r}_2^{(1)}, \ldots, \boldsymbol{r}_N^{(1)} \right\} \tag{2}$$

and another chain

$$\left\{ \boldsymbol{r}_1^{(2)}, \boldsymbol{r}_2^{(2)}, \ldots, \boldsymbol{r}_N^{(2)} \right\}. \tag{3}$$

A permanent cross-link of the i'th bond on chain 1 with the j'th bond on chain 2, for example, requires that the condition

$$\boldsymbol{r}_i^{(1)} = \boldsymbol{r}_j^{(2)} \tag{4}$$

holds for all possible polymer conformations. There is one such constraint for each cross-link, of course.

A field-theoretical treatment introduced by Edwards (Edwards and Freed, 1970a,b; Edwards, 1988; Boué et al., 1988) resolves some of the issues related to enforcing and generating the cross-linking in the mathematical formulation of the gel. The method is based on the Gaussian functional integral expression for a complex field:

$$\mathcal{N} \int [d\varphi][d\varphi^\star] \prod_{i=1}^{M} \varphi(\boldsymbol{r}_i) \prod_{j=1}^{M} \varphi^\star(\boldsymbol{R}_j) \, e^{- \int d\boldsymbol{r} \, \varphi(\boldsymbol{r}) \varphi^\star(\boldsymbol{r})}$$
$$= \sum_{\text{pairs}} \delta(\boldsymbol{r}_{l_1} - \boldsymbol{R}_{m_1}) \delta(\boldsymbol{r}_{l_2} - \boldsymbol{R}_{m_2}) \ldots \delta(\boldsymbol{r}_{l_M} - \boldsymbol{R}_{m_M}). \tag{5}$$

The expression above contributes two important aspects to pairwise linked systems. It simultaneously enumerates all possible ways of linking N sites in space *and* enforces the cross-links through the delta functions.

It is now possible to use these fields to produce cross-links (Fantoni and Müller-Nedebock, 2011). The method can be applied in the closed multimerisation scenario (Nyrkova and Semenov, 2005). With f-functional cross-linkers a complicated-looking theory for the cross-

link constraints emerges:

$$Z_N = \mathcal{N} \int [d\varphi][d\varphi^\star] \left\{ \prod d\boldsymbol{R} \right\} \left\{ \prod G \right\}$$
$$\exp\left(-\int d\boldsymbol{r}\, \varphi(\boldsymbol{r})\varphi^\star(\boldsymbol{r}) + \right.$$
$$\int d\boldsymbol{r}\, \rho(\boldsymbol{r}) \ln(\varphi^\star(\boldsymbol{r})/d) + z_1 \int d\boldsymbol{r}\, \varphi(\boldsymbol{r})$$
$$\left. + z_f \int d\boldsymbol{r}\, \varphi^f(\boldsymbol{r}) \right). \qquad (6)$$

Z is the partition function that is related to Helmholtz free energy F and the temperature T of Equation (1) through

$$\frac{F}{k_{\mathrm{B}}T} = -\ln Z. \qquad (7)$$

One can show that a saddle-point approximation (frequently used in such field theories) always leads to exactly one physical result.

Although it might not seem obvious by inspection of the equations above, the correct enumeration of all permissible realisations of the disorder *as well as* of the constraints the disorder imposes on the polymer degrees of freedom is addressed in the formalism above.

In a recent paper (Fantoni and Müller-Nedebock, 2011) the clustering by so-called Janus particles was described. These particles have a rather specific interaction that favours clustering of the particles in certain, limited multiples or functionalities. When Janus particles are coupled to a chain, reversible networks form. The field-theoretical formalism outlined above can be used to characterise the degree of clustering and the resultant stability against a collapse transition for the Janus chains.

The field theory can be implemented in useful manner in scenarios where cross-links are permanent, but is also evidently useful for reversible cross-linking. Indeed this has interesting repercussions for systems in which there are charged polymers and counter-ions (such as the charged DNA in Figure 2). It is known that highly valent counter-ions can cause salt bridges similar to the scenario in Figure 1, but that ions can also simply condense on chains without necessarily causing bridging. Recent calculations using the formalism indicate that the classification and identification of the various electrostatic roles of counter-ions is possible and leads to a single formalism that includes several possible effects. It is possible to identify the amount of charge condensation on chains, the degree to which the salt bridges cause a local attraction, as well as the degree of screening that is prevalent in the system. As for the Janus particles, the complicated-seeming formalism provides exactly one physical solution under all conditions.

3.3 Confining networks and enforcing topology

Two additional aspects of the polymer networks are worth examining and remain widely open questions. The first is that the network is contained within some confining volume – such as the cytoskeleton that occupies the small volume of a cell. Most analytical treatments of polymer networks impose an averaged deformation on the system and do not study in detail how the network behaves at its boundaries. Boundaries will couple to the orientations of filaments (Müller-Nedebock et al., 2003), influencing the possible conformations of the network.

The second challenge to theorists is that cross-linking may introduce closed loops of polymers. As one knows from normal pieces of string, the possibility exists that the polymers are knotted. For example, the simple trefoil knot in Figure 7 cannot turn into any other type of knot unless the loop itself is broken.
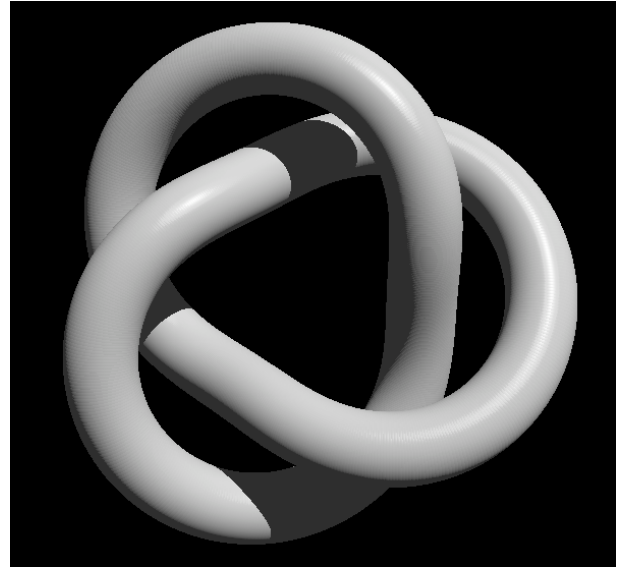

Figure 7: A trefoil knot must remain a trefoil knot unless it is cut open.

Similary, the Borromean rings in Figure 8 must stay co-localised. The conservation of the state of knottedness of loops is non-local, i.e. it depends on the whole path the polymer chain follows, which imposes some severe challenges for a suitable statistical physical approach (Müller-Nedebock and Edwards, 1999; Edwards and Müller-Nedebock, 1999).
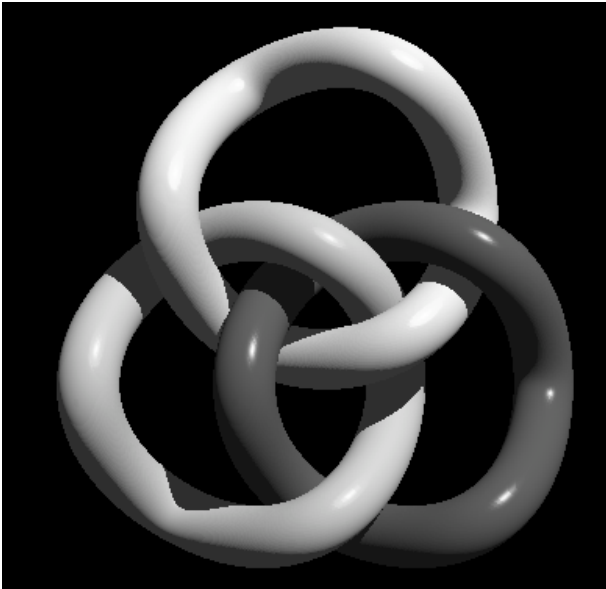
Figure 8: Borromean rings are not entangled with each other when viewed as pairs, but the triplet of rings definitely is entangled.

One possible scenario is depicted in Figure 9 where the entanglement of the strand seems to indicate some localisation. This has been modelled as a "slipping link" (Ball et al., 1981).
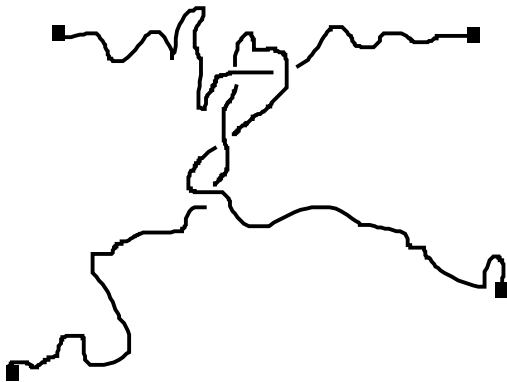

Figure 9: Entanglement of one strand of network with another.

Both these challenges of topology and confinement are currently being addressed at Stellenbosch University.

4 Networks out of equilibrium

4.1 Molecular motors

Molecular machines are responsible for a huge variety of biological functions. The machines utilise chemical energy in the form of adenosine triphosphate (ATP) to produce forces, rotation or other types of motion. Physicists have investigated the interesting mechanisms of the function of molecular machines for the past two decades (Jülicher and Prost, 1995; Jülicher et al., 2007).

The actin filaments and microtubules mentioned earlier act as tracks for the motion of some types of the molecular motors. Various types of myosins can move along actin filaments and kinesins and dyneins are responsible for transportation along microtubules. Since both types of filaments consist of assembled dimers these filaments have inherent directions, or *polarity*. Motors will consistently prefer to move along the filaments in a preferential direction. Figure 10 shows a cartoon of a kinesin walking along a microtubule. Myosins typically exert forces by attaching, exerting a power stroke and then detaching from the filament (cf. Figure 11).
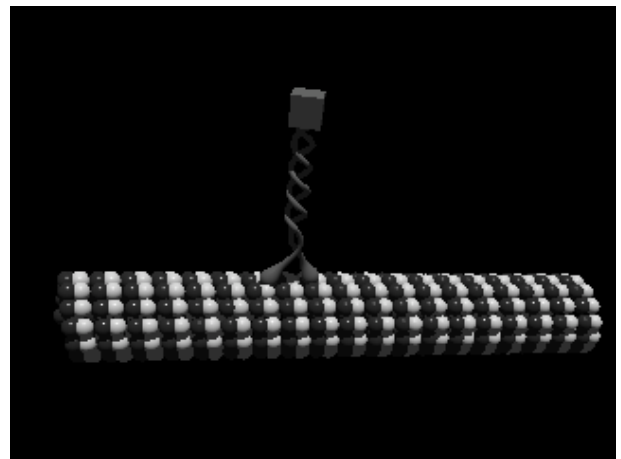

Figure 10: A schematic of kinesin on a microtubule. The load or attachment occurs where the cartoon shows a square.

Such motors utilise chemical energy and exert local forces, which means that the equilibrium formalism for statistical physics as discussed in the preceding section is mostly inapplicable to these types of systems. A dynamical statistical physical formulation becomes requisite in most cases. The reader might not be surprised to learn that dynamical formalisms for networks, and especially networks where machines might exert forces, pose significant challenges to both theorists and experimentalists.
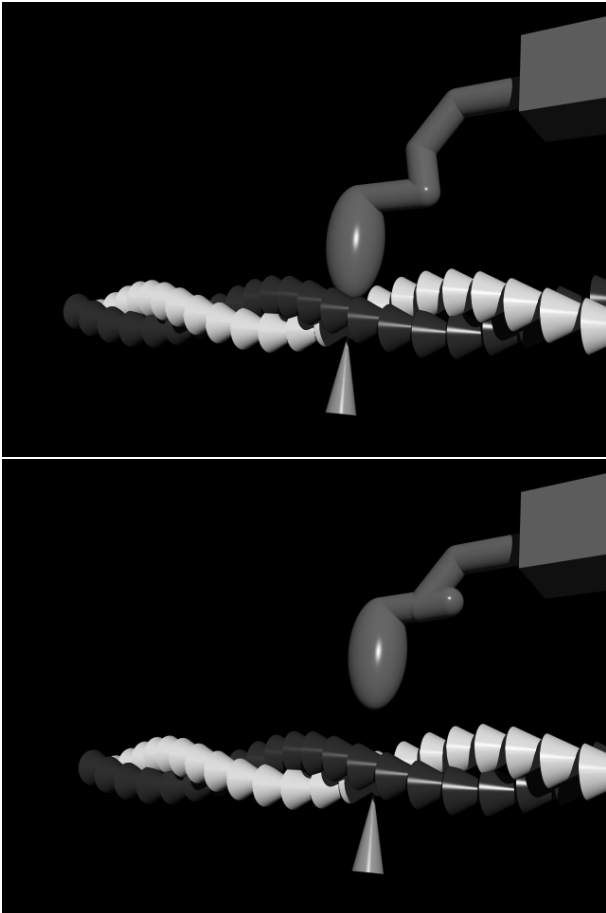
Figure 11: Myosin motors are associated with actin filaments. The stepping action differs from that of kinesins.

4.2 Molecular machines as linkers

How then would molecular machines affect the properties of a network of filaments? One scenario is that pairs of motor heads link two filaments in much the same way as a cross-link. However, depending on the orientation of the underlying filament, the motor head will exert a force and start to move in a specific direction, whereas the other head, attached to another filament, might pull in a completely different direction. The results of this should be that additional stresses now emerge in the network. An example is depicted in Figure 12. The arrows indicate the directions in which the motors prefer to travel along the filaments. (It is the orientation of the filament together with the type of motor that determines the direction of the motion.) In the scenario depicted the motors pull in opposite directions, stretching the tether connecting the two motor heads and (statistically) causing the filaments to bunch up in their wakes. The ends of the two strands consequently experience an additional attractive force that is caused by the pulling action of the motors. If the filaments

were aligned in parallel such that both motor heads travel in the same direction the behaviour would be less interesting. Apart from moving along the filaments the whole *active* cross-link might also become detached, diffuse around the network and attach elsewhere.

Networks which contain molecular motor pairs as cross-linkers are referred to as *active gels*. The computation of their properties is of great current interest in the biophysics community. A two-stranded system coupled by motors was investigated by Liverpool and coworkers (Liverpool et al., 2009). The researchers concluded on the *contractile* behaviour the motors cause in a two-stranded system.
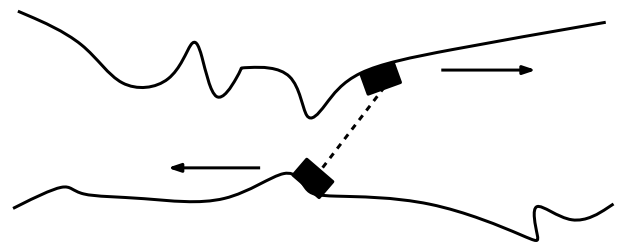

Figure 12: A schematic representation of two motors (blocks) that are tethered to each other (dotted line) pulling along the preferential directions (arrows) given by the orientation of the filaments.

The system of Liverpool and coworkers was also the inspiration of two Master's theses, by Mohau Mateyisi and Karl Möller, at Stellenbosch University in the past years (Mateyisi, 2011; Möller, 2011).

Using the ideas and the formalism of the motor as slipping link (referred to earlier in the discussion on topology), but now with preferential positioning along the filament according to a force that is dependent on the displacement along the filament, it is possible to construct a minimal model for force-applying, permanently attached cross-links. The resulting calculations show that such a system can have a non-monotonic force-extension relationship. This is due to the force-exerting slipping link relocalising from near the end of a filament – where it is cross-linked permanently to other filaments – to a more central position. This also yields completely different elastic coefficients. Further calculations draw on the work of Edwards (Deam and Edwards, 1976) to conclude on the role of disorder in such networks.

Cross-links that move in a preferential direction are of course dynamical. The simple two-stranded (or effectively single-strand) system can also be modelled using a Langevin equation, where the directed diffusion of the motor attachment point $\sigma(t)$ is joined with a

dynamically fluctuating filament $r(s,t)$:

$$\gamma \frac{\partial r(s,t)}{\partial t} = -\frac{\delta H}{\delta r(s,t)} + f(s,t) \qquad (8)$$

$$\gamma' \frac{\partial \sigma(t)}{\partial t} = -\frac{\delta H}{\delta \sigma(t)} + f'(t) + \phi_{\mathsf{m}} . \qquad (9)$$

The Hamiltonian H models the chain and the motor tether elasticity with stochastic forces f and f', and ϕ_{m} indicates the motor force. The coupled equations enable the derivation of a steady state for the motor system and lead to conclusions on the fluctuations of the motor position and forces in the filament.

The model described above do not allow for the motors to become detached. However, a good model will need to account for detachment of motors due to stochastic effects or as induced by forces in the system. In some situations motor clusters rather than single motors produce the traction forces on filaments, which requires the description of multiple states of the motors comprising the cluster as shown in Figure 13.
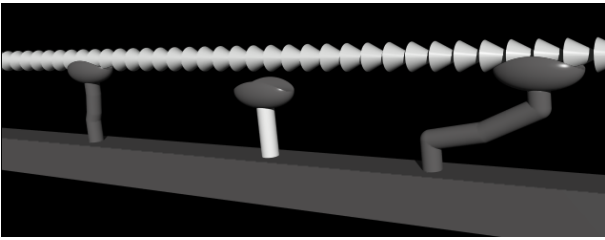

Figure 13: Two attached motors, one stretched and another detached motor in a cluster near a filament.

5   Continuing the quest

Many biological systems in the course of the processes of life have some structures or functions where the potential additional understanding brought about by using the methods of statistical physics may prove to be extremely useful. New and amazing experimental techniques take the theoretical physicist's enterprise far beyond the hypothetical, enabling the testing and informing of models and theories.

The daily discoveries of novel complexity and yet more beauty astound and fascinate us. They nourish our enthusiasm to learn more and to disentangle the clues of how the world works.

Thanks

My deepest gratitude goes to all my dedicated teachers, lecturers, supervisors, mentors and colleagues for their inspiration and encouragement. I am extremely grateful and privileged to have thought about physics with exceptionally gifted students and collaborators.

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