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STUDY OF NUMERICAL MODEL OF INTERACTIONS BETWEEN FILAMENTS AND LINKER

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ABSTRACT

A detailed understanding of biopolymer networks can be considered a corner stone for future developments in many fields of modern science and engineering ranging from biophysics and biochemistry to bioengineering, biomedical engineering and material science. Biopolymer networks consist of three essential components: filaments, cross linker molecules connecting them by chemical bonds, and a viscous fluid into which filaments and cross linker molecules are embedded. These three components are modelled as continua. On the level of single filaments, the laws of statistical mechanics have significant impact to the equations of motion. In this paper the three interactions i.e. chemical interactions, contact interactions and long range electrostatic interactions are further explained.

Keywords: biopolymer networks, cross linker, filaments, interactions, linkers.

I. INTRODUCTION

Biopolymer networks are formed by three main constituents: polymer filaments, cross linker molecules (referred to also as 'linkers') which connect these filaments by transient chemical bonds, and a background fluid into which filaments and linkers are embedded. The background fluid is typically an aqueous solution and therefore nearly transparent. The size of the linkers on the other hand ranges on the nanometre scale. The variety of completely different network architectures which can be formed by one and the same kind of filament just by the application of different linkers is remarkable. Not only fluid, filaments, and linkers have to be modelled, but rather also the interactions between them. The same is true also for linkers, of course. Thus, only interactions between filaments and linkers remain to be discussed. In experiments so far three main types of such interactions have been observed:

(I) Chemical interactions,

(II) Contact interactions,

(III) Long-range electrostatic interactions.

Chemical interactions lead to the formation of chemical bonds between linkers and filaments and turn thereby free linkers into singly bound ones and singly bound linkers into doubly bound ones. These bonds are in general only temporary and disaggregate after a while stochastically owing to thermal fluctuations. Such unbinding events turn doubly bound linkers into a single bound ones and a single bound linkers into a free ones. Contact interactions play an important role when filaments and linkers come close to each other and prevent them from overlapping. Physically, they are short-range electrostatic interactions. In addition to that, in principle also long-range electrostatic interactions may result from the fact that filaments and linkers are in general electrically charged. It is often doubted that long-range electrostatic interactions play an important role in biopolymer networks, because the charge of filaments and linkers is supposed to be shielded on long distances quite effectively by ions in the surrounding fluid. Yet the results of certain experiments [1] raise the question, whether there are not at least certain cases where long-range electrostatic interactions play a role in biopolymer networks. Thus, long range electrostatic interactions are listed in this section as potential interaction type between filaments and linkers noting that in practice they may often or even always play only a minor role. Thereforealtogetherthreetypesofinteractionsareingeneraltobemodeledinsimulations of biopolymer networks.

II. NUMERICAL MODEL OF INTERACTIONS BETWEEN FILAMENTS AND LINKERS

2.1 Chemical Interactions

Filaments and linkers may interact with each other by chemical bonds which transmit forces and moments. In the following, we will assume that such bonds arise only between one filament and one linker, respectively. Direct chemical bonds between two filaments or two linkers will not be discussed as in biopolymer networks such bonds are typically assumed either not to arise at all or not to matter. It is emphasized, however, that the quantitative considerations below about bonds between one filament and one linker can be directly applied also to chemical bonds between two filaments or two linkers if this required in some special case in the future.

To form a chemical bond, a linker L and a free filament binding site F have to be sufficiently close to each other, i.e., the linker has to be within the so-called reaction volume V_{react} of the binding site. Once this is the case, both molecules can form a bond if they reach a proper relative position and orientation. In a very short time interval Δt, where the probability of multiple binding and unbinding events is negligible, this can be modelled by a Poisson process with a so-called on-rate $k_{react,on}$, and the probability for binding can be computed by: -

$$p_{on} = 1 - \exp(-k_{react,on}\Delta t) \quad (1.1)$$

Similarly, unbinding of a linker already bound to a filament happens with an off-rate $k_{react,off}$ and the probability: -

$$p_{off} = 1 - \exp(-k_{react,off}\Delta t) \quad (1.2)$$

In computer simulations based on the method introduced in the preceding sections, filament and linker positions are known at each point in time. Thus for a numerical model of chemical interactions between filaments and linkers, one just has to define the position of the binding sites on the filaments and their respective reaction volume.

In principle, a binding site may be any point on the filament. In reality, binding sites are usually periodically distributed over filaments with a characteristic distance h_{bind}. If filaments are discretized with finite elements, the simplest way of modelling binding sites is setting the finite element discretization length h equal to h_{bind} and defining the finite element nodes as the binding sites of the filament. This allows for modelling doubly bound linkers just as finite beam or truss elements connecting two already existing nodes in the filament discretization.

Modelling the reaction volume is possible in various ways. It seems reasonable assuming that free linkers can react with binding sites, if the distance between the linker centre $x_{cl,c}$ and the binding site ranges in the interval $[(R_{cl} - \Delta R_{cl})/2; (R_{cl} + \Delta R_{cl})/2]$. Singly bound linkers on the other hand can bind to another binding site only if the distance of this binding site and the one they are already attached to ranges in the interval $[R_{cl} - \Delta R_{cl}; R_{cl} + \Delta R_{cl}]$. By means of these two distance criteria one can decide whether a linker is in the reaction volume of a binding site.

This model can be extended easily by additional geometric constraints refining the definition of the reaction volume. A comprehensive discussion of such constraints would go beyond the scope of this thesis, however, at least one example seems worth being discussed: it is well known that certain types of linkers can connect only filaments in certain relative orientations. The linker fascin, e.g., can link only almost parallel filaments [2], whereas the linker alpha actinin is flexible and rather in sensitive towards the orientation of the linked filaments [2]. This can be modelled by a simple orientation constraint: singly bound linkers are assumed to be in the reaction volume of a free binding site only if the angle between the filament on which this binding site is situated and the filament to which the linker is already attached to ranges in the interval $[\phi - \Delta\phi; \phi + \Delta\phi]$. Here φ may be considered as preferred binding angle and Δφ as tolerance around it. The angle between the filaments can be computed in a finite element model either from the triads representing the cross section orientation of the filaments or alternatively from the tangents to the three dimensional curves representing their neutral lines. Both ways are expected to lead to almost identical results as shear deformation is usually negligible due to the high slenderness ratios of typical biopolymers.

For simulations, the parameters $k_{react,on}$ and $k_{react,off}$ have to be specified. Various data sources can be used to this end. The most important one are experiments such as presented in [3, 4] where the on- and off-rates k_{on} and k_{off} of the bimolecular reaction: -

$$L + F \underset{k_{off}}{\overset{k_{on}}{\longleftrightarrow}} LF \tag{1.3}$$

are determined. Here LF is the species of linkers bound to a filament binding site. Denoting the molar concentration of a species by [.], the number of binding and unbinding events per unit time and volume is given by definition of the on- and off-rates by k_{on}[L][F] and k_{off} [LF], respectively [5]. From the experimentally determined k_{on}, one can immediately compute the parameter $k_{react,on}$ required in simulations. In view of (1.1), the expected number of binding events per time and filament binding site is given by the on-rate $k_{react,on}$ times the number of linkers in the reaction volume of a certain binding site, which is [L] V_{react}. To get the total number of binding events per volume, one has to multiply this term with the concentration of filament binding sites per volume, i.e., with [F], which leads to

$$k_{react,on}[L]V_{react}[F] = k_{on}[L][F] \tag{1.4}$$

And thus

$$k_{react,on} = \frac{k_{on}}{V_{react}} \tag{1.5}$$

With

$$k_{react,off} = k_{off} \tag{1.6}$$

Simulation parameters can then directly be determined from the experimentally measured on-and-off rates of the bimolecular reaction (1.3). It is emphasized that in order to get a simulation parameter $k_{react,on}$ consistent to the experimentally measured kon, not the real reaction volume is required in (1.5), but just the one used in the simulations. In case that experimental results are available only for either kon or koff, the respective other rate constant can be computed according to [5] by

$$\frac{k_{react,on}}{k_{react,off}} = \exp\left(-\frac{\Delta G_{L+F\to LF}}{k_B T}\right) \tag{1.7}$$

If at least the binding energy $\Delta G_{L+F\to LF}$ is known. If no experimental data is available for a certain linker-filament combination, MD simulations are another data source for on-and-off rates or binding energies.

In [6, 7] a similar model for chemical interactions between filaments and linkers is proposed. There, however, chemical bonds are assumed not to form with some probability p_{on}, but rather always if the linker is in the reaction volume of the filament and both have the proper relative orientation. The definition of the proper relative orientation for the reaction to happen requires some geometric parameters and tolerances. These are hard to determine in practice by experiments or MD simulations, which is a serious drawback of this approach. Furthermore, this model assumes that motion of filaments and linkers can be simulated by a micromechanical model sufficiently exactly down to the length and time scale relevant for chemical reactions. In reality, however, chemical reactions often happen on much a faster time scale and are furthermore affected by geometric or electrostatic properties on much a smaller length scale than considered in a micromechanical model.

In reality, the probability of unbinding increases significantly according to Bell's formula [5], if a chemical bond is loaded by forces or moments. This effect is not captured by the above model, where bond life time is assumed not to depend on the load transmitted by the bond. Especially, for biopolymer networks in the nonlinear regime, this effect may play an important role so that an extension of the above model incorporating Bell's formula may be useful in the future. In practice, this is possible easily by making the off-rate for doubly bound linkers dependent on their internal forces and moments according to Bell's formula.

An avenue of future research might be the exploration of additional constraints for the definition of the reaction volume besides just distance and filament orientation. In reality, binding sites are situated on one side of the filament so that bonds to free linkers may be impossible if these are on the opposite side of the filament owing to the filament backbone forming a solid barrier between binding site and linker. This effect as well as geometric details of the position of the binding sites on the filaments depending on the filament type could be accounted for by advanced orientation constraints in the future. It is emphasized that already in [6, 7] it was tried to account for the geometry of the binding sites in a similarly detailed manner by means of a Frenet-Serret frame, but that the formalism developed there is actually mathematically incorrect in case of general deformation, because of the singularity of the Frenet-Serret frame for straight filaments. Detailed modelling of the geometry of filament binding sites distinguishing between different directions orthogonal to the filament backbone is indeed in general possible only by means of a filament discretization providing material triads such as a finite element discretization or an especially enriched bead-spring discretization [8, 9].

2.2 Contact Interactions

Mechanical contact between filaments and linkers poses kinematic constraints to filament and linker motion which can be accounted for as usual in finite element simulations [10]. In the equations of motion, contact forces can be accounted for by deterministic external forces. As linkers are typically much smaller than filaments, the volume of free and singly bound linkers may either be neglected completely in contact computations or modelled as ball around the linker centre or binding site to which the linker is attached. Doubly bound linkers are represented by beam elements and their volume can be accounted for in contact computations accordingly. If free and singly bound linkers are neglected, contact can be modelled exclusively as what is referred to in finite element textbooks and articles as beam contact. In principle, the methods described there can be directly applied to biopolymer networks.

In studies of single polymers, contact interactions play a role only if the polymer is flexible enough for self-contact. This is expected to be the case only for so-called flexible polymers whose length L is much larger than their persistence length L_p, whereas for semi-flexible polymers with L ≈ L_p and stiff polymers with L << L_p self-contact is not expected. For the equilibrium thermodynamics of networks consisting of (infinitesimally) thin filaments and linkers, contact interactions do interestingly not play any role at all: in thermodynamic equilibrium, the probability of a certain network configuration depends only on its free energy, and for infinitesimally thin filaments the difference between the free energy of a system with and without excluded volume effects is almost surely equal to zero.

2.3 Long-range electrostatic Interactions

Both filaments and linkers in biopolymer networks may exhibit an electric charge. For actin filaments, e.g., the linear charge density is 4e/nm [11]. This charge may on the one hand affect the effective stiffness of filaments. In more complex cases, it may on the other hand cause long-range interactions between different filaments and linkers or just different segments of one and the same filament or linker. Additionally, the electric charge may entail complex ionic patterns in the surrounding fluid shielding it partially. For biopolymer networks, the situation is more complicated. So far, no evidence has been presented that electrostatic forces play a major role for their mechanics itself. However, diffusion of charged particles [1] through networks or the network architecture in the presence of certain linker types [12] may be significantly affected by electrostatic effects beyond just an altered filament stiffness. Therefore, for the time being, the incorporation of electrostatic effects by means of simple effective stiffness's seems reasonable.

III. CONCLUSION

In this paper, the three different types of interactions taking place between linkers and filaments are presented. The mechanics of filaments is assumed to dominate the mechanics of the networks, and thus only coarse models are employed for linkers and fluid. In chemical interactions filaments and linkers may interact with each other by chemical bonds which transmit forces and moments, in contact interactions mechanical contact between filaments and linkers possess kinematic constraints and in long range electrostatic interactions both filament and linker in the biopolymer network exhibit electric charge.

REFERENCES

1. O. LIELEG, I. VLADESCU, K. RIBBECK, Characterization of particle translocation through mucin hydrogels, Biophys J 98(2010) 1782–1789.
2. D.S. COURSON, R.S. ROCK, Actin crosslink assembly and disassembly mechanics for alpha-actinin and fascin, Journal of Biological Chemistry 285 (2010) 26350–26357.
3. W. GOLDMANN, G. ISENBERG, Analysis of filamin and [alpha]-actinin binding to actin by the stopped flow method, FEBS Letters 336(1993) 408–410.
4. S.B. MARSTON, The rates of formation and dissociation of actin-myosin complexes. Effects of solvent, temperature, nucleotide binding and head-head interactions. Biochem. J. 203(1982) 453–460.
5. J. HOWARD, Mechanics of Motor Proteins and the Cytoskeleton, Sinauer Associates, Sunderland, 2001.
6. T. KIM, W. HWANG, R. KAMM, Computational analysis of a cross-linked actin-like network, Experimental Mechanics 49(2009) 91–104.
7. T. KIM, W. HWANG, H. LEE, R.D. KAMM, Computational analysis of viscoelastic properties of crosslinked actin networks, PLoS Comput Biol 5(2009) e1000439.

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8. G. CHIRICO, Torsional-bending infinitesimal dynamics of a dna chain, Biopolymers 38 (1996) 801–811.
9. G. CHIRICO, J. LANGOWSKI, Kinetics of dna supercoiling studied by brownian dynamics simulation, Biopolymers 34(1994) 415–433.
10. P. WRIGGERS, Computational Contact Mechanics, Wiley, New York, 2002.
11. M. HOSEK, J.X. TANG, Polymer-induced bundling of f actin and the depletion force, Phys. Rev. E 69(2004) 051907.
12. I. BORUKHOV, R. BRUINSMA, Raft instability of biopolymer gels., Phys Rev Lett 87 (2001) 158101.