Mathematical Modelling of the Contribution of Mechanical
Inhomogeneity in the Myocardium to Contractile Function

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Abstract. Earlier we developed a mathematical model of the cardiac muscle that
allowed for inactivation through the effects of cooperativity of contractile proteins.
In the present work we used the model to analyze the mechanical function of an in-
homogeneous myocardium. To simulate the latter we chose, as the simplest system,
a duplex in which muscles with different mechanical properties were connected in
series and in parallel. Numerical experiments showed that the basic effect due to
the inhomogeneity consists in the non-additivity of the mechanical characteristics
of the muscle, e.g., of the relationship between end-systolic length and end-systolic
force \((L_{es} - P_{es})\). As a rule, non-additivity consists in a negative inotropic effect.
The analysis showed that the cause of non-additivity is redistribution of loads be­
tween muscles (in a parallel duplex), redistribution of lengths (in a serial duplex),
changes in the rate of contraction of each muscle compared to contraction that when
working separately, shifts in time to \(L_{es}\). Also, the model predicts that additional
inactivation of contractile proteins in a muscle within a duplex against isolation
is the substantial mechanism of enhanced non-additivity. Among the factors of in­
homogeneity studied the basic determinants are difference in amplitudes between
isometric tensions developed by each muscle in isolation and the asynchronism in
the development of these tensions.

Key words: Muscle contraction and relaxation — Mathematical model — Muscle
duplex

Introduction

The fundamental mechanics of the cardiac muscle has been established on the
basis of the assumption that all of its functional units are mechanically identical.

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Recently, however, a growing body of evidence has shown that this assumption may be wrong (Markhasin et al 1994b). Moreover, some types of inhomogeneity (e.g., asynchronism) seem to be important characteristics of the contractile act. Thus, sarcomeres have been shown to elongate asynchronously during the relaxation cycle (Edman 1980).

Inhomogeneity may be present in the contractile structures of the myocardium in a variety of forms ranging from variations in property from one cross-bridge to another (Morgan 1985) to differences in the contractile characteristics between whole segments of the heart chambers (Pandian et al 1983, Markhasin et al 1994a,b).

In pathological conditions the inhomogeneity of the contractile function may be greater than in normal condition (Markhasin et al 1994a,b). Thus, during the systole an ischemic area in the myocardium may be subject to a mechanical wave of a complicated shape (Weyman et al 1984).

Inhomogeneity produces a considerable effect on the pumping and contractile functions of the heart. Thus, inhomogeneities of segmentary contractions were observed to increase dramatically in dilatational myocardopathy or cardiac aneurysms, impairing markedly the pumping and contractile functions of the heart (Markhasin et al 1994a,b). Contrary to expectations, local activation of a segment in the wall of the left ventricle by adrenaline was found (Lew and Rasmussen 1989) to result in a longer, rather than shorter, ventricular relaxation time constant, which provides evidence that inhomogeneity alone can disturb the lusitropic characteristics of the myocardium.

Thus, mechanical inhomogeneities are important complex phenomena which require special experimental and theoretical study. Because mechanical inhomogeneities are so complicated we believe that while at an early stage studies should be based on simple modelling systems such as muscles duplexes composed of parallel or series fragments of an isolated myocardium.

The first study of this kind was undertaken by Tyberg et al (1969) who studied the mechanical behaviour of a system of two papillary muscles connected in series during asynchronous isometric and isotonic contractions and under conditions of hypoxia created for one of the muscles. The authors estimated the length-force relationship for isometrically contracting duplexes disregarding the possibility of changes in its slope in muscles interacting within a duplex, which is essential for the understanding of the mechanisms of this interaction.

The authors of another work (Wiegner et al 1978) simulated a duplex consisting of a hypoxic and a normal myocardium connected in series. First the computer memorized the isotonic contractions of the muscle under normal conditions. This muscle was then subjected to hypoxia and was made to contract under load applied by the computer which remembered the isotonic contractions of the normal muscle. In this case, obviously, there was no feedback between the normal and the hypoxic...
Our experiments (Izakov et al. 1991, Markhasin et al. 1994b) had a different design. We investigated real interactions between two parallel papillary muscles simulating contractions of an intact muscle (physiological mode). The mechanical characteristics were first recorded separately for each of the muscles and then within a duplex of the same muscles. The motropic conditions of the muscles working separately and within the duplex were estimated by the length-force dynamic relationship measured as the relation between the end-systolic length and the end-systolic force of the muscles. The interaction of the muscles was estimated as follows: first we computed the Formal Length – Force Relationship (FLFR) as a formal sum of the length – force relationships for each of the muscles contracting separately, i.e., tensions developed by the muscles were summed up for each end-systolic length, and the resulting FLFR was compared with the real length – force relationship for these muscles connected in a duplex.

The results revealed two types of interactions between inhomogeneous muscles in a duplex: additive, where FLFR agreed with the real one, and non-additive, where there was no agreement. In the latter case FLFR could lie above the real relationship (negative motropic inhomogeneity effect) or below it (positive motropic inhomogeneity effect). It was not clear what mechanisms were responsible for the sign and the extent of motropic inhomogeneity effects.

Mechanical inhomogeneities are very complicated myocardial phenomena. Since the contractile elements of the myocardium may differ in the slope of the length – force – velocity relationships as well as in the intensity and duration of the activated condition, it is extremely difficult to estimate the contributions of each of these differences to the contractility of an inhomogeneous myocardium. It seems reasonable, therefore, to parallel these experiments with mathematical modeling of cardiac muscle contractions. It is important, however, that models used reproduce a sufficiently broad and characteristic range of mechanical phenomena in the myocardium. The use of models for theoretical investigation of the contribution of a mechanical inhomogeneity to the contractile function of the myocardium provides a unique opportunity to study the role of specific contractile parameters in the determination of the sign and the extent of non-additive effects by varying the corresponding parameters in the model. Should this approach work out well, it will make possible a prediction of, e.g., how chemomechanic processes in the various layers of the cardiac muscle should be designed to ensure optimal functioning.

We developed a mathematical model of cardiac muscle contractions which reproduces various mechanical phenomena in it (Katsnelson et al. 1990, Izakov et al. 1991). This model was used to analyse mechanical effects in parallel and series muscles duplexes. This paper presents the results of numerical experiments on the duplex model based on the varying of different model parameters.
Mathematical Model

The modelling of series and parallel duplexes depends essentially on the choice of the base model, i.e., the set of equations describing each of the elements of a duplex whereby each of these elements is characterised by its own set of values, and interactions between them are represented by relationships added to the basic equations.

For series connection these relationships are given by

(i) $P_1 = P_2$ and $L_1 + L_2 = \text{const}$ for isometric contractions

(ii) $P_1 = P_2 = D = \text{const}$ for the isotonic mode

For parallel connection the relationships added are somewhat different

(i) $L_1 = L_2 = \text{const}$ for isometric contractions

(ii) $L_1 = L_2$ and $P_1 + P_2 = D = \text{const}$ for the isotonic mode

where $P_1, L_1$ are the tension and length of the first muscle, $P_2, L_2$ are those of the second muscle, while $D$ is afterload.

The physiological mode of duplex contraction is described similarly with the only difference that during the isotonic phase afterload $D$ may incorporate impedance, in this case rather than being constant it depends on the length of the duplex and its velocity of shortening.

Thus, the main problems in modelling a duplex are associated with the choice of a suitable base model for the homogeneous module.

We proceed from the assumption that such a model should provide a very subtle simulation of the basic effects observed in physiological experiments on the mechanics of homogeneous myocardium. It is particularly important that this model correctly reproduce feedbacks between the mechanical characteristics of a contracting homogeneous module and its activation. The fact is that within a duplex two muscles may exhibit a considerable redistribution of lengths (series connection) and loads (parallel connection). The above-mentioned feedbacks, therefore, can make a substantial contribution to the resulting behaviour of each of the muscles and of the duplex as a whole.

Based on these considerations we chose our earlier published model (Izakov et al. 1991) as our base model. It allows for the above-mentioned feedbacks assuming two types of cooperativity for contractile proteins.

Cooperativity of the first type assumes that the dissociation rate of calcium-troponine complexes depends on the concentration of cross-bridges attached to the thin filament near these complexes. The higher the concentration, the lower the rate.

Cooperativity of the second type means that the dissociation of a calcium-troponine complex slows down with the increasing concentration of such complexes near it along the thin filament.
Originally, we developed a model using the first type of cooperativity only (Katsnelson et al 1990) However, it is the inclusion of both cooperativities that enabled us to simulate the entire range of important phenomena such as mechanochemical uncoupling effects (Izákov et al 1991) (load-dependent relaxation, the response of the muscle to fast cyclic deformations, the dependence of the slope of the normalised length-tension curve on the level of intracellular calcium, etc ) The equations of the base model were introduced and substantiated elsewhere (Katsnelson et al 1990, Izákov et al 1991) We, therefore, skip these equations and proceed directly to numerical experiments Note only that we use the variant of the model published in Circulation Research (Izákov et al 1991) In this paper the equations are given in Appendix 1 in a strictly formal programmable form without any physiological background Appendix 2 contains the basic parameters, while Table 1 contains parameters modified to enable the simulation of the second muscle connected in an inhomogeneous duplex with the muscle described by the basic set of parameters

Table 1. Parameters modified to enable the simulation of the second muscle connected in a non-homogeneous duplex with the muscle described by the basic set of parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Basic values</th>
<th>Modified values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>$14.6 , \mu m^{-1}$</td>
<td>$5.5 , \mu m^{-1}$</td>
</tr>
<tr>
<td>$V_{\text{max}}$</td>
<td>$0.0043 , \mu m , ms^{-1}$</td>
<td>$0.00215 , \mu m , ms^{-1}$</td>
</tr>
<tr>
<td>$g_1$</td>
<td>Characteristics of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$0.4 , \mu m^{-1}$</td>
<td>$0.6 , \mu m^{-1}$</td>
</tr>
<tr>
<td>$g_2$</td>
<td>Probability $n_1(t_1)$</td>
<td>$0.4$</td>
</tr>
<tr>
<td>$t_d$</td>
<td>$170 , ms$</td>
<td>$120 , ms$</td>
</tr>
<tr>
<td>$Ca_m$</td>
<td>$0.045$</td>
<td>$0.225$</td>
</tr>
<tr>
<td>$c_{20}$</td>
<td>$0.2 , ms^{-1}$</td>
<td>$0.4 , ms^{-1}$</td>
</tr>
</tbody>
</table>

Results of Numerical Experiments

Numerical experiments were performed for inhomogeneous systems of two types In the first case the object of study was the mechanical behaviour of an inhomogeneous duplex consisting of two muscles connected in parallel In the second case we investigated a model of two muscles connected in series In both cases the mechanical characteristics recorded were the time course of isometric contractions in each of the muscles, the length–force relationship, and the time course of the relaxation cycle Additionally we studied the time course of the activation of
contractile proteins by calcium. All of these relationships were examined for each muscle separately and for the same muscles combined in an inhomogeneous duplex.

When combining muscles in a duplex we used a model of two muscles where one was a reference described by the basic set of parameters while the other presented the same set with one of the parameters modified.

To analyse the contribution of a mechanical inhomogeneity to the contractile function of the myocardium we varied the following parameters of the model:

\[ V_{\text{max}} \] - the maximum rate of shortening under zero load,
\[ C_{\text{m}} \] - the maximum amplitude of free intracellular calcium,
\[ t_\text{d} \] - the duration of the calcium transient,
\[ c_{20} \] - the rate constant of calcium-troponin complexes dissociation,
\[ g_1, g_2 \] - parameters of the probability of cross-bridge attachment depending on the distance between the thin and the thick filament.

Additionally, we varied the parameters responsible for the stiffness of the parallel elastic element.

The reference was a homogeneous muscle model with basic parameter values as given in Appendix 2.

On plots of length \( L \) versus time and on those of \( L_{\text{es}} - P_{\text{es}} \), the values plotted on axis \( L \) and \( L_{\text{es}} \) were sarcomere elongations (of the duplex) with respect to the idle length of an inactivated non-elongated sarcomere, which is taken to be 1.8 \( \mu \)m (for the duplex the idle length is 3.74 \( \mu \)m).

**Parallel duplex**

In this section, we deal with the modeling of the duplexes composed of two cardiac muscles connected in parallel and contracting as a whole in either isometric or physiological mode under a load exerted to the duplex end.

The physiological mode consists of four sequential stages of the contraction – relaxation cycle:

- isometric contraction at the initial length, lasting until the duplex tension achieves the level of the exerted load,
- contraction under this load with the additional loading impedance, lasting until the duplex achieves maximum shortening (end-systolic length \( L_{\text{es}} \)). The impedance changes proportionally to the shortening velocity,
- isometric relaxation at the new length (\( L_{\text{es}} \)), lasting until the duplex tension achieves its initial passive level corresponding to the initial duplex length,
- relaxation in a special mode when the duplex is elongated with a constant velocity until it achieves the initial length.

Except \( L_{\text{es}} \), the following terms will be further used:

\( P_{\text{es}} \) - end-systolic tension of the duplex (of the muscle within the duplex),
\( V_{\text{max}} \) - for any muscle of the duplex this term means the velocity of its individual unloaded shortening.
Figure 1. Development of isometric tension at $L_{\text{max}}$ during the contraction-relaxation cycle for parallel duplexes: strong homogeneous (1), weak homogeneous (2), non-homogeneous (3) A non-homogeneous as to $V_{\text{max}}$ B non-homogeneous as to $n_{1}(1)$ C non-homogeneous for $C_{\text{adm}}$ D non-homogeneous for $t_{d}$ E inhomogeneous for $c_{20}$ F non-homogeneous as to SE (Series elasticity)

$t_{30}$ is the duplex (or the muscle) tension decay time to 30% of its maximum value.

Fig 1 shows isometric contractions at length $L_{\text{max}}$ for a homogeneous reference duplex, for a homogeneous duplex with one of the parameters modified (Table 1), and for a non-homogeneous duplex.

Fig 1A presents the results of a numerical experiment with modified $V_{\text{max}}$. 
Figure 2. Length-force relationship for a parallel duplex non-homogeneous as to $V_{\text{max}}$ (3), for the stronger (4) and weaker (5) muscles forming this duplex, for the same stronger (1) and weaker (2) muscles within homogeneous duplexes, formal sum (6).

Note that changing of this parameter brings about a reduction in the amplitude of isometric contractions in a homogeneous duplex. At the same time the plot shows a weak distinction in the time course of the isometric tensions up to the peak. On the other hand, it features a shorter characteristic time of relaxation $t_{30}$.

In a non-homogeneous duplex the amplitude of isometric contractions (curve 3) takes an intermediate position.

Fig. 2 shows end-systolic length ($L_{es}$) versus end-systolic force ($P_{es}$) in the physiological mode of loading modelled for the reference muscle in a homogeneous duplex (curve 1), for a muscle with reduced $V_{\text{max}}$ in a homogeneous duplex (curve 2), for the same muscles contracting in a non-homogeneous duplex (curves 4,5), and for a non-homogeneous duplex as a whole (curve 3). Also, Fig. 2 shows the $L_{es}$-$P_{es}$ relationship calculated as a formal sum (curve 6) of curves 1 and 2. The formal sum was obtained by totaling $P_{es}$ over curves 1 and 2 for each value of $L_{es}$.

The comparison shows a difference between the $L_{es}$-$P_{es}$ relationships calculated for each muscle incorporated in the homogeneous and non-homogeneous du-
plex. Thus, for a given $L_e$, the stronger muscle develops a weaker force in the homogeneous duplex as compared with the non-homogeneous one. These differences are small and are virtually nil in the range of 2.13 μm to 2.17 μm. They are even less for the weaker muscle. At the same time, $P_e$ is markedly less in the non-homogeneous duplex for $L_e$ from 2.18 μm to 2.24 μm as compared with the value obtained by formal summation. This means that muscles combined in a non-homogenous parallel duplex interact in a non-additive way producing a negative inotropic effect. At the same time a mechanical inhomogeneity associated with a large difference in $V_{\text{max}}$ between the muscles exhibits an additive effect over a great range of lengths $L_e$ (from 2.08 μm to 2.17 μm).

Fig. 3 shows the results of numerical modelling of a single contraction-relaxation cycle in an inhomogeneous duplex in physiological mode. As before, the inhomogeneity was simulated by decreasing $V_{\text{max}}$ for one of the muscles.

Fig. 3A presents curves for changes in length of:
- a homogeneous strong duplex (1)
- a non-homogeneous duplex (2)
- a homogeneous weak duplex (3)

Fig. 3B presents curves for changes in tension of:
- a muscle in a homogeneous strong duplex (1)
- a strong muscle in a non-homogeneous duplex (2)
- a weak muscle in a homogeneous duplex (3)
- a weak muscle in a non-homogeneous duplex (4)
- a non-homogeneous duplex (5)

Homogeneous duplexes were selected for each of the muscles so as to have the same afterload on this muscle at the onset of the shortening for both homogeneous and non-homogeneous duplexes. The point in time at which shortening begins in both duplexes (indicated by the simple arrow in Fig. 3) is also the same. The double arrow points to the moment at which the non-homogeneous duplex stops to shorten. As may be seen from Fig. 3A, this moment is not much different from the points in time at which $L_e$ is achieved in each of the homogeneous duplexes. Thus, the elements of the non-homogeneous parallel duplex composed of muscles differing in $V_{\text{max}}$ contract virtually synchronously in physiological mode as well. This synchrony may account for the additive effect observed for the length force curves over a great range of $L_e$ values. Fig. 3B shows that the weak muscle is in isotonic condition almost throughout the shortening phase, i.e., the stronger muscle bears all the additional load associated with the impedance in the non-homogeneous duplex. It has to develop, therefore, a stronger force in a non-homogeneous duplex as compared with a homogeneous one. In contrast, impedance causes a greater force to be developed by the weaker muscle in a homogeneous duplex.
Figure 3. Shortening (A) and tension development (B) in a parallel duplex non-homogeneous as to $V_{\text{max}}$ and in corresponding muscles within this duplex and in homogeneous systems. Physiological mode of loading. See the text for more details.

Fig. 4 illustrates calcium activation of contractile proteins in the above contraction-relaxation cycle (by activation we mean the concentration of calcium-troponine complexes).

4A – the course of activation of the stronger muscle in a homogeneous (curve 1).
Figure 4. Time course of variation in the concentration of CaTn in a contraction-relaxation cycle for the physiological mode of loading. A CaTn in the stronger muscle in a homogeneous parallel duplex (1), CaTn in the stronger muscle in a parallel duplex non-homogeneous as to $V_{\text{max}}$ (2) B CaTn in the weaker muscle in a homogeneous duplex (3), CaTn in the weaker muscle in a duplex non-homogeneous as to $V_{\text{max}}$ (4)

and non-homogeneous (curve 2) duplex
4B the course of activation of the weaker muscle in a homogeneous (curve 3) and non-homogeneous (curve 4) duplex

Some difference in the course of activation of each muscle between the homogeneous and non-homogeneous cases may be seen in the decay phase. In general
this difference is not large, the weaker muscle exhibits some additional inactivation in the non-homogeneous duplex as compared with the homogeneous one, while the stronger muscle shows the opposite. Nevertheless, the role of this difference at the end of the systole becomes significant: the non-homogeneous duplex reaches its end-systolic length at 320 ms during the activation decay phase of both muscles. In Fig 4 this moment of time is marked by the double arrow. By this time a majority of calcium-troponin complexes in the weaker muscle has broken down, and by the end of the systole of the weaker muscle in the non-homogeneous duplex the difference in activation between the homogeneous and non-homogeneous cases amounts to almost 50%. By the same moment in time additional activation of the stronger muscle in the non-homogeneous duplex reaches 20% (with respect to the homogeneous case). Thus, the redistribution of loads in a non-homogeneous duplex is related to the course of activation in both muscles. Moreover, the redistribution of loads changes the other mechanical characteristics of the muscles (sarcomere lengths and rates of shortening, above all) and affects the course of activation through the cooperativity mechanisms of the contractile proteins. The modified activation, in turn, enhances the redistribution of loads, enabling the stronger muscle to develop additional force and making the weaker muscle still weaker.

Figs 1B and 5, 6, 7 present the results of numerical modelling of a parallel duplex composed of muscles differing in \( g_1 \) and \( g_2 \), which characterise \( n_1(l_1) \), the dependence of the probability of cross-bridge attachment on sarcomere length.

As may be seen from Fig 1B, which shows the course of isometric contractions at length \( L_{\text{max}} \), the muscles differ in the amplitude of the tension developed but also in the time course of tension development. Thus, the difference in the time to peak of the isometric tension is 80 ms, i.e. the muscles work in asynchrony. The stronger (reference) muscle is slower (curve 1), while the weaker and faster muscle exhibits a steeper dependence \( n_1(l_1) \) than the reference one.

Fig 5 shows the plot of end-systolic length versus force. In contrast to the previous case, the weaker muscle in this non-homogeneous duplex is weaker than in the homogeneous one over the entire range of lengths \( L_{es} \), while the stronger muscle is stronger. Also, there is a non-additive effect over the entire range of lengths \( L_{es} \) for the non-homogeneous duplex as a whole. As in the first case, this effect is negative. Non-additivity, observed over the entire range of lengths \( L_{es} \) (and thus distinguishing this non-homogeneous variant from the previous case) is, primarily, a consequence of a more prominent asynchrony in the contraction of both muscles. This kind of asynchrony is also seen in Fig 6, which shows the time course of tension development and length change for a homogeneous and a non-homogeneous duplex during a single contraction-relaxation cycle in physiological conditions. One manifestation of asynchrony observed in the physiological mode of loading in Fig 6 consists in the following: When the non-homogeneous duplex...
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Figure 5. Length-force relationship for a parallel duplex non-homogeneous as to $n_1(l_1)$ (3), for the stronger (4) and weaker (5) muscles forming this duplex, for the same stronger (1) and weaker (2) muscles operating in homogeneous duplexes, formal sum (6).

achieves $L_{es}$ (marked by the double arrow in Fig 6) its force attains the maximum (see curve 5) Apparently each muscle of this duplex should reach its end-systolic length at the same moment of time since they shorten within the duplex in parallel, and yet neither of the muscles is at its peak tension at this moment Moreover, tension continues to grow rather intensively in the stronger muscle and reaches maximum only in 40 ms, while the weaker muscle has already been undergoing relaxation for 40 ms by the end-systolic length.

Fig 7 shows calcium-troponine activation curves corresponding to these processes. The difference between the activation curves for homogeneous and non-homogeneous duplexes is less significant than in the first variant of inhomogeneity (according to $V_{max}$). By the time the non-homogeneous duplex achieves $L_{es}$ the difference in activation amounts to about 20% in the weaker muscle and to about 8% in the stronger muscle. The direction of differences in the tension and activation of each muscle between homogeneous and non-homogeneous duplexes agree (Figs 6B and 7) and are similar to those observed for inhomogeneity as to $V_{max}$. Thus, for an inhomogeneity of the $n_1(l_1)$ type the parallel duplex develops a relationship be-
Figure 6. Shortening (A) and tension development (B) in a parallel duplex non-homogeneous as to \( n_1(l_1) \) and its component muscles operating within this duplex and in homogeneous systems. Physiological mode of loading. The numbering of the curves is similar to that in Fig. 3.

between the redistribution of loads and the time course of activation similar to that observed for a \( V_{\text{max}} \) type inhomogeneity. True enough, in this case the contribution
Figure 7. Time course of variation in the concentration of CaTn in a contraction-relaxation cycle for the physiological mode of loading.  

A. CaTn in the stronger muscle in a homogeneous parallel duplex (1), CaTn in the stronger muscle in a parallel duplex non-homogeneous as to $n_1(l_1)$ (2), B. CaTn in the weaker muscle in a homogeneous duplex (3), CaTn in the weaker muscle in a duplex non-homogeneous as to $n_1(l_1)$ (4)

of additional activation to the decay of the tension developed by the weaker muscle in a non-homogeneous duplex is less significant than for the $V_{\text{max}}$ inhomogeneity
Figure 8. Length-force relationship for a parallel duplex non-homogeneous as to the series elasticity SE (3), for the stronger (4) and weaker (5) muscles forming this duplex, for the same stronger (1) and weaker (2) muscles operating in homogeneous duplexes, formal sum (6)

Also, additional activation of the stronger muscle in the non-homogeneous duplex is weaker. Even so, the non-additive effect is more prominent where contraction exhibits marked asynchrony.

Numerical modelling of parallel duplexes non-homogeneous as to $Ca_m, t_d, c_{20}$ provided absolutely similar qualitative results as the above variant of $n_1(l_1)$ inhomogeneity. In all the cases (see Fig. 1C, D, E) the contraction-relaxation cycle was faster in the weaker muscle, which led to an appreciable asynchrony. Of special interest (as is shown below) was the case of two parallel muscles whose inhomogeneity was due to a radically different compliance of the series elastic elements. The results of numerical modelling of this type of inhomogeneity are shown in Fig. 1F and Figs. 8, 9, 10. Fig. 8 reveals the fundamental difference of this variant of inhomogeneity from all of the above cases. It shows the relationship between end-systolic lengths and corresponding tensions in homogeneous and non-homogeneous duplexes. As can be seen from the relative positions of curves 3 and 6, this variant of inhomogeneity (the only one of all those studied in the work) leads to a positive...
Figure 9. Shortening (A) and tension development (B) in a parallel duplex non-homogeneous as to the series elasticity SE, and in its muscles operating within this duplex, and in homogeneous systems. Physiological mode of loading. The numbering of the curves is similar to that in Fig. 3.

Inotropic effect, i.e., the P_{es} of a non-homogeneous duplex occurs above the formal sum of the corresponding values of P_{es} for a weak and a strong muscle combined in a homogeneous duplex over the entire range of L_{es} values.
Figure 10. Time course of variation in the concentration of CaTn in a contraction-relaxation cycle for the physiological mode of loading. A CaTn in the stronger muscle in a homogeneous parallel duplex (1), CaTn in the stronger muscle in a parallel duplex non-homogeneous as to SE (2). B CaTn in the weaker muscle in a homogeneous duplex (3), CaTn in the weaker muscle in a duplex non-homogeneous as to the series elasticity SE (4).

**Series Duplex**

In this section we deal with the modelling of duplexes formed by two cardiac muscles connected in series and contracting as a whole in either isometric or physiological mode under a load exerted to the duplex end.
Figure 11. Isometric tension development at $L_{\text{max}}$ in a contraction-relaxation cycle in series duplexes strong homogeneous (1), weak homogeneous (2), non homogeneous (3)

A non-homogeneous as to $V_{\text{max}}$  B non-homogeneous as to the series elasticity SE  C non-homogeneous as to $c_{20}$  D non-homogeneous as to $C_{a_m}$  E non-homogeneous as to $t_d$  F non-homogeneous as to $n_1(t_1)$

Physiological regime as well as all the terms used below have been already defined in the previous section.

Fig. 11 shows the results of modelling of isometric contractions (for $L_{\text{max}}$) in a series homogeneous reference, a series homogeneous duplex with one of the parameters changed (see Appendix 3 for the list of parameters), and a non-homogeneous duplex.

Fig. 11A illustrates curves for isometric contractions obtained by changing the parameter $V_{\text{max}}$. As in the case of parallel connection, tension development here exhibits a high degree of synchrony.
Figure 12. Length-force relationship for a series duplex non-homogeneous as to $V_{\text{max}}$ (5), for the stronger (1) and weaker (2) muscles operating in isolation, for a strong (3) and weak (4) homogeneous duplex composed of these muscles, formal sum (6) agrees in this case with curve 5 demonstrating additive effect.

Fig. 12 shows end-systolic force $P_{cs}$ versus the corresponding length $L_{cs}$ for the physiological mode of loading modelled for the reference muscle in a homogeneous series duplex (curve 1), a muscle with reduced $V_{\text{max}}$ contracting in a homogeneous series duplex (curve 2), homogeneous duplexes (curves 3 and 4), and an inhomogeneous series duplex composed of these muscles (curve 5). Additionally, Fig. 12 shows the $L_{cs}-P_{cs}$ relationship calculated as a formal sum of curves 1 and 2. The formal sum was obtained differently than in the case of parallel connection, i.e., $L_{cs}$ were summed for each value of $P_{cs}$. The results of summation are marked in Fig. 12 by the circles. The curve for the formal sum (curve 6) passing through these circles shows a close fit to curve 5. Fig. 12 does not present the length of each muscle.
Figure 13. Tension development (A) and shortening (B, C) in a series duplex non-homogeneous as to $V_{\text{max}}$ and in its muscles operating within a duplex and in isolation. Physiological mode of loading. See the text for the description of the curves.

contracting within the non-homogeneous duplex versus the end-systolic length because this relationship has no meaning for series connection. This is explained in detail below.

Fig 12 shows also that the capacity of a non-homogeneous duplex to develop tension declines as compared with the stronger muscle and increases as compared with the weaker muscle (see the position of curve 5 in relation to curves 3, 4). Muscles in such a non-homogeneous duplex work in an additive manner; the formal sum of curves fits curve 5 precisely. As in the case of the parallel connection this
additivity results primarily from synchronous operation of the muscles differing in the value of $V_{\text{max}}$ only.

Fig. 13 shows the results of numerical modelling of a single contraction-relaxation cycle in physiological mode of loading for a series duplex non-homogeneous as to $V_{\text{max}}$. Fig. 13A shows the development of tension in such a cycle for a homogeneous reference muscle (curve 1), a homogeneous weak muscle, i.e., a muscle with reduced $V_{\text{max}}$ (curve 2), and a non-homogeneous series duplex composed of these muscles (curve 3). It is evident that curve 3 represents tension development in each of the muscles forming a non-homogeneous duplex since in series connection the tensions developed by the muscles agree between them and with the tension developed by the duplex as a whole. The arrow on the ordinate points to afterload 40 common for the three cases. As can be seen from this Figure, the muscles operate in almost complete synchrony under physiological loading as well. The tension of the stronger muscle in a series non-homogeneous duplex drops while that of the weaker muscle increases. Fig. 13B shows the time courses of the non-homogeneous duplex shortening and elongation corresponding to the time course of tension the duplex develops as represented by curve 3 in Fig. 13A. The length vs time curve is fairly typical for the physiological mode. Meanwhile, each of the muscles in the duplex exhibits complicated redistribution of lengths as can be seen from Fig. 13C. The latter shows length vs time curves for:

- a strong homogeneous muscle (1),
- a weak homogeneous muscle (2)
- the stronger muscle in a non-homogeneous duplex (5)
- the weaker muscle in a non-homogeneous duplex (6)

As may be seen from this Figure, the muscle length variation curve for the homogeneous case is completely different from that describing the variation of its length for the same afterload in a non-homogeneous duplex. In a series non-homogeneous duplex each muscle executes a complicated oscillating motion. Moreover, the muscles shorten in parallel from the time of afterload (160 ms) to the beginning of isometric relaxation at a new length (330 ms). Starting at 720 ms both muscles extend passively under the external force which restores the duplex at a constant velocity to its original length. During the other intervals the muscles operate in opposite phases: one of them shortens while the other one elongates, the weaker muscle outpulling the stronger one between 320 and 560 ms (the duplex relaxing at a new constant length). Starting at 600 ms both muscles are completely inactivated (see Fig. 14) and redistribution of lengths takes place between the passive parallel elements.

The course of activation shown in Fig. 14 (changes in the concentration of calcium-calponin complexes) corresponds to the above contraction-relaxation cycles of both muscles. Fig. 14A presents the course of activation of the stronger homogeneous muscle (curve 1) and the stronger muscle in a non-homogeneous se-
Figure 14. Time course of variation in the concentration of CaTn in a contraction-relaxation cycle for the physiological mode of loading. 

A. CaTn in the stronger muscle working alone (1), CaTn in the same stronger muscle in a series duplex non-homogeneous as to $V_{\text{max}}$ (2) 

B. CaTn in the weaker muscle in a series duplex non-homogeneous as to $V_{\text{max}}$ (3) CaTn in the same weaker muscle working separately (4)
shown in Fig. 13C the stronger muscle is shorter over the greater part of the cycle in a non-homogeneous duplex than in isolation, the weaker one being, by contrast, longer. In accordance with the model assumptions a decrease in length results in a quicker dissociation of calcium-troponine complexes (which is observed in the stronger muscle) while an increase slows this process down (as in the weaker muscle). Hyperactivation of the weaker muscle, in turn, adds more tension to it in a non-homogeneous duplex. In a duplex the stronger muscle, on the contrary, develops a somewhat weaker tension, which is also in agreement with the tendency towards reduction of its activation.
Figure 16. Tension development (A) and shortening (B C) in a series duplex non-homogeneous as to the series elasticity SE and in its muscles operating within the duplex and separately. Physiological mode of loading. The numbering of the curves is similar to that in Fig 13.

Numerical experiments with a series duplex whose series elements feature non-homogeneous stiffness (Fig 11B and Figs 15, 16, 17) provide results which are very close to the additive effect although the range of common values of $P_{es}$ required to construct a formal sum is too small to enable one to draw an ultimate reliable conclusion regarding the additivity of the curves relating the end-systolic tension to the corresponding length (Fig 15). Nevertheless the suggestion of additivity is
Figure 17. Time course of variation in the concentration of CaTn in a contraction-relaxation cycle for the physiological mode of loading. A CaTn in the stronger muscle working separately (1) CaTn in the same stronger muscle in a series duplex non-homogeneous as to the series elasticity SE (2) B CaTn in the weaker muscle working separately (3) in the same weaker muscle in a series duplex non-homogeneous as to SE (4)

confirmed by a very close fit of the time course of isometric tension development in both muscles to a synchronous one despite a considerable difference in amplitude
Figure 18. Length-force relationship for a series duplex non-homogeneous as to $c_{20}$ (5) for the stronger (1) and weaker (2) muscles of this duplex working separately for a strong (3) and a weak (4) homogeneous duplex composed of these muscles, formal sum (6).

(Fig 11B) In physiological mode these muscles contract also nearly in synchrony, which can be seen in Fig 16A.

Fig 11C and Figs 18,19,20 show the results of a numerical experiment with a series duplex non-homogeneous as to the dissociation rate of calcium-troponine complexes $c_{20}$. Fig 11C demonstrates the considerable asynchrony in the isometric contractions of the duplex components working separately (curves 1 and 2). This asynchrony leads to a marked delay in the final stage of the relaxation phase (curve 3). As a result of the asynchrony the non-homogeneous duplex exhibits a negative inotropic effect (curves 5 and 6 in Fig 18). Also asynchronous are muscles in the physiological contraction-relaxation cycle, which can be seen in Fig 19A. Fig 19C suggests that the weaker muscle operates at lengths exceeding its original length.
Figure 19. Tension development (A) and shortening (B,C) in a series duplex non-homogeneous as to c20 and its muscles working within the duplex and separately. Physiological mode of loading. The numbering of the curves is similar to that in Fig 13.

throughout the greater part of the active phase in the cycle. At the time of the end-systolic force (280 ms) this muscle extends rather than shortens (curve 6). The stronger muscle, by contrast, continues to shorten up to 400 ms, reducing in length between 280 ms and 400 ms by nearly the same value as from the beginning of
Figure 20. Time course of variation in the concentration of CaTn in a contraction-relaxation cycle for the physiological mode of loading. A. CaTn in the stronger muscle working separately (1), CaTn in the same stronger muscle in a series duplex non-homogeneous as to $c_{20}$ (2). B. CaTn in the weaker muscle in a series duplex non-homogeneous as to $c_{20}$ (3), in the same weaker muscle working separately (4).

The cycle to 280 ms. Thus, coinciding with the point in time at which the non-homogeneous duplex reaches its shortest length the time of the end-systolic force of this duplex is in no way related to the points in time at which the weaker or stronger muscles forming this duplex reach their shortest dimensions. Neither do the points in time at which these muscles reach their shortest dimension in the course
of contraction in a non-homogeneous duplex agree between themselves. Moreover, there have been experiments in which the original length of the weaker muscle in a series non-homogeneous duplex is its minimal length at all. Therefore curves relating the end-systolic force to the lengths these muscles reach in the course of their contraction in a series non-homogeneous duplex could not be meaningfully interpreted.

Numerical modelling of series duplexes inhomogeneous as to \( \text{Ca}_{\text{m}}, t_d, \) and \( n_l(l_1) \) provides the same qualitative results as the experiment with inhomogeneity as to \( \epsilon_{20} \). In particular, muscles differing in the indicated parameter always exhibit marked asynchrony when operating in isolation. Connected in a series non-homogeneous duplex these muscles demonstrate a negative inotropic effect in all of the above cases.

**Discussion**

Let us summarise the results obtained by numerical modelling of non-homogeneous series and parallel duplexes.

The contribution of a mechanical inhomogeneity to the contractile function of the myocardium was studied for both non-homogeneous systems by varying alternatively one of the model parameters listed above (see Results of Numerical Experiments).

The non-homogeneous system represented by a duplex with muscles connected in parallel exhibited non-additivity in the form of a negative inotropic effect in all cases with the exception of inhomogeneity as to the stiffness of the series element. In other words, the length – force relationship for a non-homogeneous duplex was found to lie below the curve representing the formal sum of length – force relationships for weaker and stronger muscles working in homogeneous systems. The weaker muscle in the model of the non-homogeneous duplex developed a weaker tension than the same muscle in the homogeneous duplex for the same end-systolic length. The stronger muscle, in contrast, got stronger in a non-homogeneous duplex. Note that within the framework of the model, inhomogeneity as to one of the parameters did not cause a high non-additivity (up to 10–15%) despite the fact that the parameter itself was varied significantly which manifested itself in a nearly twofold difference in the amplitude of isometric contractions between non-homogeneous muscles at \( L_{\text{max}} \) (see Fig 1). At the same time variation of different model parameters revealed certain peculiarities of the non-additivity discovered. Thus variation of \( V_{\text{max}} \) did not bring about non-additivity over the entire range of end-systolic lengths. The degree of non-additivity most strongly depended on the time course of tension development in each of the non-homogeneous muscles.

Non-additivity was the greater, the greater the asynchrony in muscle contraction.

Since non-additivity is the most general and most striking manifestation of
inhomogeneity the question arises as to its mechanism. Some light is thrown on the mechanism when one compares the mechanical behaviour of each of the muscles in a homogeneous and a non-homogeneous duplex during the contraction-relaxation cycle. The body of facts presented clearly shows that substantial redistribution of loads takes place in each of the muscles upon their inclusion in a non-homogeneous duplex. This redistribution, in turn, leads to a change in the rate of shortening of each of the muscles as compared with the rate of their shortening within a homogeneous system. As a result, the time it takes to reach specific values of $L_{es}$ also changes. Regardless of the inactivation phenomenon, the change in the time to $L_{es}$ alone should lead to a change in the ability of the muscle to develop an active effort at a given length. In other words, even if the model did not account for the mechanism of inactivation, the curve $L_{es}-P_{es}$ for each of the muscles would be shifted in a homogeneous system such that a weaker muscle would become even weaker while the stronger muscle gets even stronger.

Although the additivity phenomenon, in principle, could be explained by shifts in the time to specific $L_{es}$ values for the muscle included in a non-homogeneous duplex, the analysis shows that this mechanism is not unique.

A change in the rate of muscle shortening in a non-homogeneous duplex due to the redistribution of loads changes the time to $L_{es}$ but also has a marked effect on the process of inactivation, which, in turn, affects further redistribution of loads. The evidence for this is provided by the results of numerical modelling shown in Figs. 1-10.

Thus the mechanism of non-additive muscle interaction in a non-homogeneous duplex comprises four closely related factors:

- redistribution of loads,
- a change in the rate of contraction,
- a change in the time to specific values of $L_{es}$,
- inactivation of contractile proteins.

In all of the cases of inhomogeneity studied non-additivity manifested itself, as a rule, in the form of a negative inotropic effect except one where positive inotropic effect was observed. Note that the negative inotropic effect occurred in systems in which the inhomogeneity was due to a difference in the properties of the contractile elements, whereas positive inotropic effect was observed in systems in which the inhomogeneity was set by changing the parameter characterising the stiffness of the series elastic element in one of the muscles. Interesting enough, despite the difference in the amplitude characteristics of the tension developed by each muscle, tension development was not so much asynchronous in time as in the experiments that provided examples of negative inotropic effect.

Although the mechanism of the positive inotropic effect observed is difficult to explain as yet, an analysis of the numerical experiment (Fig. 8) suggests that within a system non-homogeneous as to the stiffness of the series elastic elements, tension
development in the stronger muscle (for all particular values of $L_{es}$) surpasses tension decay in the weaker muscle.

The above example seems important because it indicates that interaction between muscular elements in a non-homogeneous system may, in principle, lead to a positive inotropie effect.

Figs 11–20 provide an insight into the nature of muscle mechanics in a series non-homogeneous duplex. Inhomogeneity in the duplex was set by changing the same parameters as in the case of the parallel connection. Muscles feature common behaviour in non-homogeneous systems of this type. Firstly, contraction is accompanied by a redistribution of muscle lengths.

Similarly, as in a parallel duplex, non-additivity (in the form of a negative inotropie effect) was brought about by asynchrony in tension development.

In the other cases we observed an additive effect (non-homogeneous in respect of $I_{max}$ and in respect of the parameter which determined the stiffness of the parallel elastic element). Thus, as in the case of parallel duplexes, asynchrony is an important factor which accounts for non-additivity.

As in the case of parallel inhomogeneity, the factor of inactivation is an important mechanism which gives rise to the non-additive effect in non-homogeneous muscles connected in series. There are, however, substantial differences in the activation effect between the two types of non-homogeneous systems. In a series duplex changes in the course of activation are caused by redistribution of lengths rather than loads, activation increasing in the weaker muscle and decreasing in the stronger one in a non-homogeneous duplex.

The modelling of duplexes of both types provides evidence that mechanical inhomogeneity may contribute to the contractile function of the myocardium, and this contribution may be quite substantial. Indeed, it was shown that a change in one parameter only may lead to an inotropie effect of 10–15%. Clearly, should the inhomogeneity be due to differences in several parameters (as is the case in reality) instead of one, these effects may be significantly stronger. This conclusion seems to be true for nonhomogeneous muscular systems represented by parallel and series duplexes. In both cases the mechanism underlying these effects is self-coordinated interaction of various factors including redistribution of lengths or loads, changes in the rate of shortening and the time to the end-systolic length, as well as changes in the activation of contractile proteins.

The simulation of the mechanical behaviour of a non-homogeneous myocardium poses a number of methodological problems. One of them is the comparison of the mechanical behaviour of a whole non-homogeneous system with the local behaviour of its members. The above facts indicate that a non-homogeneous system as a whole behaves qualitatively as a homogeneous system. In other words, such a duplex exhibits shortening, tension development and the length–force relationship similar to those observed for homogeneous muscles, being in accordance with the
expectations) intermediate between corresponding curves for homogeneous strong and weak duplexes. At the same time, each muscle in a non-homogeneous duplex may show a substantially different behaviour from that of a homogeneous system. It is particularly evident for muscles connected in series.

This observation is important because the energy needs of the myocardium were shown to be closely related to the area delineated by the deformation-tension curve (Suga et al. 1985). It is, therefore, clear that despite qualitative similarity between the global characteristics of a homogeneous and a non-homogeneous myocardium, the local characteristics of segments in a non-homogeneous cardiac muscle may be important for determining energy consumption in this area of the myocardium which in turn affects the efficiency of the system as a whole. On the other hand, if no special efforts are made to eliminate inhomogeneities in experiments, every experimental object will be inhomogeneous. Nevertheless, the similarity of the characteristics of homogeneous and inhomogeneous muscles suggests that experiments performed on these objects taken as a whole provide qualitatively correct conclusions as to the behaviour of homogeneous muscles.

A serious methodological problem is the construction of the relationship between the end-systolic length and force for each of the muscles contracting within a non-homogeneous duplex since the end-systolic length and the end-systolic force are achieved at different times in each of these muscles. In a parallel connection the \( L_{es} \) of the duplex coincides with the \( L_{es} \) of each of the muscles contracting in the duplex, and these lengths are achieved at the same time as the \( L_{es} \) of the whole duplex, however, each muscle achieves \( P_{es} \) at its own point in time. The weaker muscle does it somewhat earlier than \( P_{es} \) of the whole duplex while the stronger does it later (sometimes significantly later).

It would be but natural to resolve this methodological problem by constructing a \( L_{es} - P_{es} \) relationship, where \( L_{es} \) is the end systolic length common for, and attained simultaneously by, the parallel duplex and its elements during the contraction-relaxation cycle, and \( P_{es} \) is the force developed by a corresponding muscle by the time \( L_{es} \) is achieved.

Reasoning by analogy one should choose for the analysis of the members of a series duplex the \( L_{es} - P_{es} \) relationship where \( P_{es} \) is the end systolic length common for, and developed simultaneously by, the series duplex and its elements during the contraction-relaxation cycle, while \( L_{es} \) is the length achieved by the corresponding muscle at force \( P_{es} \). In this case, however, the situation is complicated by the fact that during the contraction phase a muscle included in a parallel duplex may elongate rather than shorten and \( L_{es} \), thus constructed, may exceed the initial length. We therefore believe that the question to what extent the length-force curve for each of the muscles in a non-homogeneous duplex may deviate from its position recorded for a homogeneous system has no meaning at all.

All of the above variants of inhomogeneities with respect to one parameter
feature one peculiarity, i.e. the ratio of the amplitudes of the tensions developed by the muscles is related in a certain manner to the type of asynchrony in the development of these tensions. Specifically, the weaker muscle has a shorter tension development (and decay) leg (see Figs 1 and 11). In the case of an inhomogeneity with respect to two or more parameters the situation is likely to be opposite, i.e. the time-to-peak of the weaker muscle may be longer than that of the stronger one. This variant is very interesting and calls for a special study since real muscles in non-homogeneous duplexes differ in several parameters at the same time.

The latter circumstance poses another problem, i.e. how to compare modelling results with the results of physiological experiments. In contrast to real duplexes we know exactly which model parameters of the members of a duplex modelled are inhomogeneous (take, e.g., the properties of real contractile proteins hidden from the observer). Our modelling, therefore, suggests a very important conclusion: the qualitative behaviour of a duplex depends on the observable properties of non-homogeneous muscles such as asynchrony and difference in the amplitudes of tension developed by the muscles rather than on the relationship between internal (hidden) parameters. Differences in such characteristics should rather be called functional inhomogeneity in contrast to the parametric one. Thus, the results of numerical and physiological experiments should be compared in the sense of the functional inhomogeneity (Izakov et al. 1990). Note that numerical and physiological experiments provide qualitatively close results in this respect.

Finally, it should be emphasised once again that the difference in the nature of the model parameters and real muscle characteristics creates identification problems in modelling and physiological experiments but it also provides additional opportunities for modelling. Thus, by setting the inhomogeneity as to a specific parameter or combination of parameters one can investigate their contribution to the behaviour of a duplex in pure form. In particular, modelling permits one to relate parametric inhomogeneity to a specific type of functional inhomogeneity. In this case, of course, the validity of the conclusions drawn will depend on the validity of the model itself. Due to this circumstance we go on developing new variants of our base model (Katsnelson and Markhasin 1996) extended by description of additional important molecular mechanisms and feedbacks responsible for mechanochemical phenomena in cardiac muscle fibers. We are going to use the new variants in our investigations of mechanical inhomogeneities of the heart muscle as well.

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Appendix 1

Complete Set of Differential Equations of the Homogeneous Model

In their final (suitable for calculations) form the equations for any single element of a duplex are given by

\[ \lambda \ p(l_1) \ A_1 \ n_2 \ n_1 (l_1) (l_1 + S_0) = \beta_1 \ [\exp(\alpha_1 (l_2 - l_1)) - 1] \]

\[ A_1 = c_1 \ \frac{Ca(t)}{1 - A_1} - c_{20} \ \exp(-q_k \ A_1) \ \Pi(n_1 (l_1) n_2) \ A_1 \]

\[ n_2 = g_n (l_1) \ [m(0) G^*(l_1) - n_2] \]

Isometric conditions for one homogeneous element of a duplex taken separately can be obtained by adding an additional equation to the above ones, i.e. \( l_2 = 0 \).

In isotonic conditions (for one separate homogeneous muscle element) it is replaced by the condition of constancy of the total afterload \( D \) on the series, and parallel elements exhibiting exponential stiffness

\[ \beta_1 \ [\exp(\alpha_1 (l_2 - l_1))] + \beta_2 \ [\exp(\alpha_2 l_2) - 1] = D (= \text{const}) \]

The latter equality can be differentiated in order to reduce this case to a set of differential equations as well.

Thus, the model of a homogeneous muscle element presents a set of four differential equations with respect to four variables \( l_1, l_2, A_1, n_2 \). These variables have the following meaning: \( l_1 \) is the difference between the current length of the contractile element and its length at rest, \( l_2 \) is the difference between the current muscle length and its length at rest, \( A_1 \) is the average concentration of calcium-tropomyosin complexes in the overlap zone of the thick and thin filaments, \( n_2 \) is the average probability that the myosin cross-bridge will attach to a discovered vacant actin center on the thin filament.

The other letter designations are used in the equations in two cases: either for variables that are expressed via these indicated six variables with the help of explicit functional dependencies defined in our previous paper (Izákov et al 1991) (e.g., \( Ca(t), n_1(l_1), \Pi(n_1(l_1)n_2) \) and others) or for constants that are model parameters (e.g., \( \lambda, c_1, c_{20}, \alpha_1, \beta_1, \alpha_2, \beta_2, t_d, V_{\text{max}}, \) etc.).

In the text (see Mathematical Model) we already have described the procedure of non-homogeneous duplex modelling on the basis of this homogeneous muscle model.

Appendix 2

The set of parameter values used in our numerical experiments (as a basic one) was taken from the published variant of our homogeneous muscle model (Izákov et al. 1991). It is as follows...
\[ \alpha_1 = 14.6 \, \mu m^{-1} \quad a_e = 0.0002 \, ms^{-2} \]
\[ \beta_1 = 1.0 \, g/mm^2 \quad C_{a_m} = 0.045 \]
\[ \alpha_2 = 14.6 \, \mu m^{-1} \quad c_1 = 0.29 \, ms^{-1} \]
\[ \beta_2 = 0.0012 \, g/mm^2 \quad c_{20} = 0.2 \, ms^{-1} \]
\[ \lambda = 30 \, (g/mm^2) \, \mu m^{-1} \quad \Pi_{\text{min}} = 0.05 \]
\[ q_1 = 0.0173 \, ms^{-1} \quad g_k = 4 \]
\[ q_2 = 0.26 \, ms^{-1} \quad g_1 = 0.4 \, \mu m^{-1} \]
\[ q_3 = 0.03 \, ms^{-1} \quad g_2 = 0.6 \]
\[ m_{(0)} = 0.87 \quad S_0 = 0.77 \]
\[ v_{\text{max}} = 0.0043 \, \mu m \, ms^{-1} \quad t_d = 170 \, ms \]

We defined all the concentrations appearing in the model equations in fractions of troponin (TnC) concentration, where \([\text{TnC}] = 7 \times 10^{-5} \, \text{mol/l}\).

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