Mathematical Model for the effect of cell mechanics on its displacement

Submitted to
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By

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Mathematical model for the effects of cell mechanics on its migration speed

Introduction:

The process of cell migration can be thought of as a spatially and temporally coordinated process of events that includes lamellipodial extension, formation of lamellipod–substratum attachments, cytoskeletal contraction and release of cell-substratum attachments at the rear of the cell. Cell migration speed is not likely to be universally limited by any one of theses processes. For example under certain conditions the rate of cell locomotion is proportional to the frequency of lamellipod extension while under others rear detachment appears to limit cell speed. At high cell-substratum adhesiveness the release of attachments and rear reaction limits cell speed but at low adhesiveness another process is the rate limiting step.

Cell migration speed is regulated by the adhesive interaction between a cell and its environment with maximum cell speed occurring at intermediate adhesiveness. At low adhesivness, cytoskeletal forces disturpt cell-substratum bonds so that the cells are unable to generate sufficient traction needed for efficient locomotion. Conversely, at high adhesiveness cytoskeletal forces are not sufficient to disrupt cell-subtratumbonds, leaving cells incapable of locomotion. At intermediate adhesiveness cytoskeletal forces roughly balance adhesive interaction so that adhesion can be maintained at the cell front but disrupted at the cell rear, permitting net cell body movement.

Cell Mechanics Model:

One of the requirements for persistent cell migration is intracellular force generation. A viscoelastic-solid model. Is used to present the cytoskeletal dynamics of a cell. Viscoelastic-solid models are appropriate for modeling the deformation of cells, which possess properties of both fluidity and stiffness. Fluidity can be modeled by linear viscous dashpots, in which stress is proportional to the rate of strain. Like wise, cell stiffness can be represented with linear elastic springs: Stress is proportional to strain by Hookean spring constant.

A schematic of the viscoelastic – solid model which represents a tissue cell. The cell is divided into three parts each has the length L/3. The inner part consist of a spring, dashpot, and contractile element in parallel. These compartments describe the cell body. The outer compartment, represents the uropod and lamellipod, also consists of dashpots and springs in parallel. These compartments include two types of springs: a spring for the intrinsic stiffness of each pseudopod and springs representing connection between the cell body and the adhesion bonds. These latter springs transmit the cell – body generated contractile force to the adhesion bonds and the underlying substratum to provide the net traction necessary for movement in the presence of bond asymmetry. Neglecting the effects of organelles, such as the nucleus and allowing the cell to deform only one – dimensionally.

The arrangement of viscoelastic elements in each compartment is essentially a limiting case of the standard viscoelastic-solid model

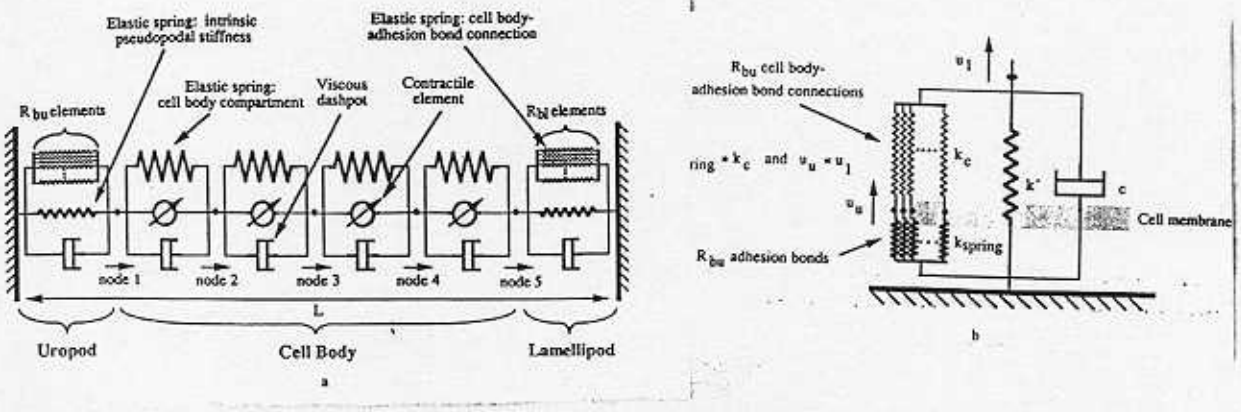

Figure (1) shows the viscoelastic – solid model which describes the cell mechanics locomotion.

The boundaries at either end of the cell are stationary see figure (1), each compartment is connected to its adjacent compartments by a node. The displacement of each node between adjacent compartments can be found by balancing the forces acting on it:

$$F_R - F_L = ma \tag{1}$$

$$\frac{dx}{dt} = V\,,\ \frac{dV}{dt} = a \tag{2}$$

Node 1

$$c\frac{dx_1}{dt} + k'x_1 + k_u x_1 = c\frac{d(x_2 - x_1)}{dt} + k(x_2 - x_1) + F_2 \tag{3}$$

Node 2

$$c\frac{d(x_2 - x_1)}{dt} + k(x_2 - x_1) + F_2 = c\frac{d(x_3 - x_2)}{dt} + k(x_3 - x_2) + F_3 \tag{4}$$

Node 3

$$c\frac{d(x_2 - x_3)}{dt} + k(x_3 - x_2) + F_3 = c\frac{d(-x_3)}{dt} + k'(-x_3) + k_l(-x_3) \tag{5}$$

$$\text{Where } k = \frac{4A_{body}E}{L},\ k' = \frac{4A_{end}E}{L},\ k_c = \frac{4A_{bond}E}{L},\ \text{and } c = \frac{4A_{body}\mu}{L} \tag{6}$$

The parameter c describes the viscosity of the dashpots, k' the intrinsic stiffness of each compartment, k_l and k_u the stiffness for the Uropod and lamelliopod, and k the stiffness of the cell body compartment. F's & x's?

The frame of reference of each node is the origin, so that at the start of contraction t = 0:

Both the uropodal and lamellipodal compartments contain elements connecting the main body of the cell to adhesion bonds. The simplest way to represent these pseudopodal elements is to assume that the stiffness of each element is proportional to the number of adhesion bonds present in each compartment:

$$k_u = k_c R_{bu} \tag{7}$$

$$k_l = k_c R_{bl} \tag{8}$$

where k_c is the stiffness contributed by cytoskeletal connection to one adhesion bond and R_{bu} and R_{bl} are the number of adhesion bonds in the uropod and lamellipod, respectively.

The number of adhesion bonds in the uropod and lamellipod can be described using simple kinetic expressions.

We assume each of these compartments as homogeneous for free and bound receptors, allowing the bounds to be uniformly stressed by the cytoskeleton. By writing the balances on the number of bounds in the uropod and lamellipod, respectively, as a function of free receptors in each compartment as

$$\frac{dR_{bu}}{dt} = k_f n_s R_{ru} - k_{ru} R_{bu} = 0 \tag{9}$$

$$\frac{dR_{bl}}{dt} = k_f n_s R_{rl} - k_{rl} R_{bl} = 0 \tag{10}$$

Where n_s is the subtratum ligand density (molecules/cm) and R_{bu} and R_{bl} are the number of bound in the uropod and lamellipod respectively.

We assume that the forward rate constant k_f is independent of the force applied to bonds, but the reverse rate constants k_{ru}, k_{rl} depend on the forces applied to bonds in the uropod and lamellipod, respectively. The rates of dissociation, are functions of the contractile energies per bond, W_u and W_l:

$$k_{ru} = \frac{k_{ro}}{\psi} e^{(W_u / k_b T)} = \frac{k_{ro}}{\psi} e^{(F_{bu} x_u / R_{bu} k_b T)} \tag{11}$$

$$k_{rl} = k_{ro} e^{(W_l / k_b T)} = k_{ro} e^{(F_{bl} x_l / R_{bl} k_b T)} \tag{12}$$

These forces F_{bu} and F_{bl} can be related to the spring constant for the connecting cytoskeleton k_c, the bond spring constant k_{spring}, the number of bonds (R_{bu} or R_{bl}) and the displacement of the bonds (x_u and $-x_l$) and cytoskeletal elements (x_l and $-x_3$):

$$F_{bu} = k_c R_{bu} x_1 = k_{spring} R_{bu} x_u \tag{14}$$

$$F_{bl} = k_c R_{bl} (-x_3) = k_{spring} R_{bl} (-x_1) \tag{15}$$

By rearranging the equations the total number of bonds in each compartment is:

$$R_{bu} = \frac{R_{Tu}}{1 + \psi \kappa^{-1} \exp\left(\frac{k_c^{\,2} u_1^{\,2}}{k_{spring} k_b T} \right)} \tag{16}$$

$$R_{bl} = \frac{R T_l}{1 + \kappa^{-1} \exp\left(\frac{k_c^{\,2} u_3^{\,2}}{k_{spring} k_b T} \right)} \tag{17}$$

The dimensionless receptor/ligand bond affinity is defined as:

$$\kappa = \frac{n_s}{K_d} \tag{18}$$

The cell's overall velocity can then be given as the average velocity of each of these nodes over a full movement cycle of extension, contraction, and relaxation:

$$\upsilon = \frac{\sum_{i=1}^{3} x_i (t = t_c)}{3 t_m} \tag{19}$$

The cell speed, in this model can be scaled as:

$$v = \frac{\upsilon}{k_{ro} L} \tag{20}$$

Equations as they appear in Madonna

```
{Top model}
{Resv} d/dt (V1) = +a1
{Resv} INIT V1 = 0
{Resv} d/dt (X1) = +V1
{Resv} INIT X1 =0
{Resv} d/dt (X2) = +V2
{Resv} INIT X2 =0
{Resv} d/dt (V2) = +a2
{Resv} INIT V2 = 0
{Resv} d/dt (X3) = +V3
{Resv} INIT X3 = 0
{Resv} d/dt (V3) = +a3
{Resv} INIT V3 = 0
F1=-2*(c*V1)-(kp*X1)-(ku*X1)+(c*V2)+(k*X2)-(k*X1)
F2=-2*(c*V2)+(c*V1)-2*(k*X2)+(k*X1)+(c*V3)+(k*X3)
F3=-2*(c*V3)+(c*V2)-(k*X3)+(k*X2)-(kp*X3)-(kl*X3)
{Flow} a1 = (F1)/M
{Flow} a2 = (F2)/M
{Flow} a3 = (F3)/M
{Conv} kp = 0.1
{Conv} c = 0.1
{Conv} kl = 0.2
{Conv} M = 0.1
{Conv} k = 0.3
{Conv} L = 10
{Conv} ku = 5
```

Parameters

Parameter	Units	Value	Definition
k_l		0.2	stiffness for the lamellipod
k_b		5	stiffness for the uropod
k_c	-	0.01	stiffness contributed by cytoskeletal connection to an adhesion bond
k_f		0.01	receptor/ligand association rate
k_{rl}		0.01	reverse rate constant for the lamallipod
k_{ru}		0.01	reverse rate constant for the uropod
k_{ro}	1/min	40	intrinsic receptor
k_{spring}	dyn / cm^2	10^{-1}	Bond spring constant
k'		0.3	intrinsic stiffness
K_d	M	10^{-7}	Equilibrium dissociation constant
c		0.1	dashpot constant
x_1, x_2, x_3	μm	0.1	Displacements of each node
A_{body}	μm^2	20	Cross-sectional area of cell body
E	dyn/cm	100	Elasticity
L	μm	20	Cell Length
μ	poise	100	Viscosity
R_{bu}	-	10	Number of Bonds on the Uopod
R_{bl}	-	20	Number of bonds on the Lamellipod
n_s	molecules/ cm	10	substratum ligend density
κ	-	0.1-10	Cell substratum adhesivness
t_m	S	$10^2 - 10^4$	Movement cycle time
t_c	S	$6.10 - 6.10^3$	Contraction time
υ	cm/sec		Cell speed
T	K		Temperature

Results

The Model equations were numerically computed by using the computer program Madonna, written by Dr. R. Macy and Dr. G. Oster. The Program is run on a Macintosh Performa 6115CD.

To understand how variations in contractile force and cell rheology affect the systems stability, several graphic experiments were studied. and a comparison between the Force and the displacement were made for the the same cells reheological properties c, kl, and ku

Test 1

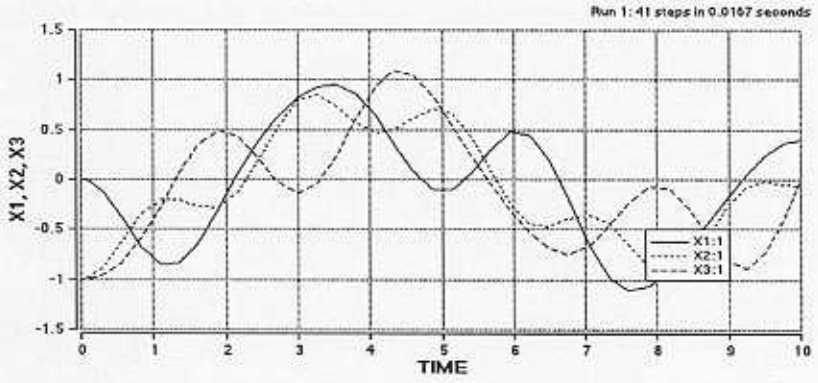

Figure (1) Relationship between Cell displacement and time for values c, kl, ku

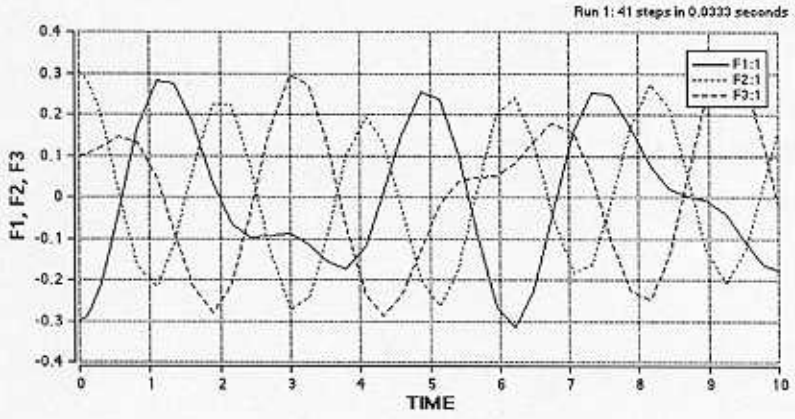

Figure (2) Relationship between the Force and time for the same values of c, kl, and ku

The values for c=0, kl=0, and ku=0, X1=0, X2=-1, X3=-1

Test 2

The Same Relationships were plotted but for a different set of values for c, kl, ku

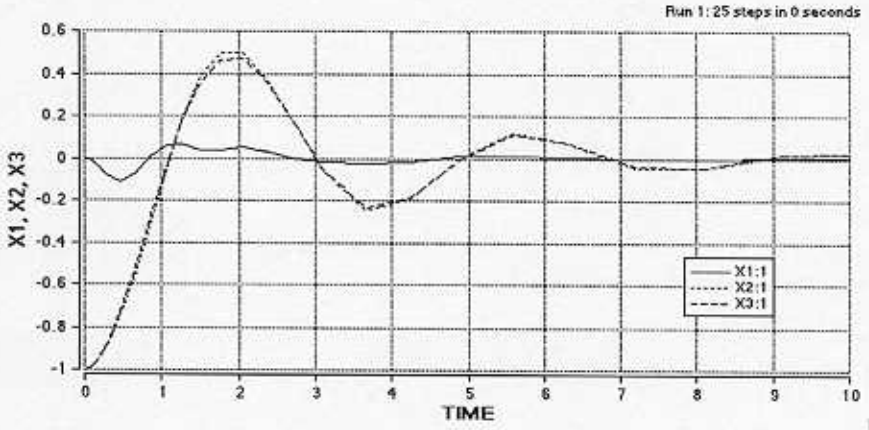

Fig (3) Displacement and Time

I would use a smaller time step.

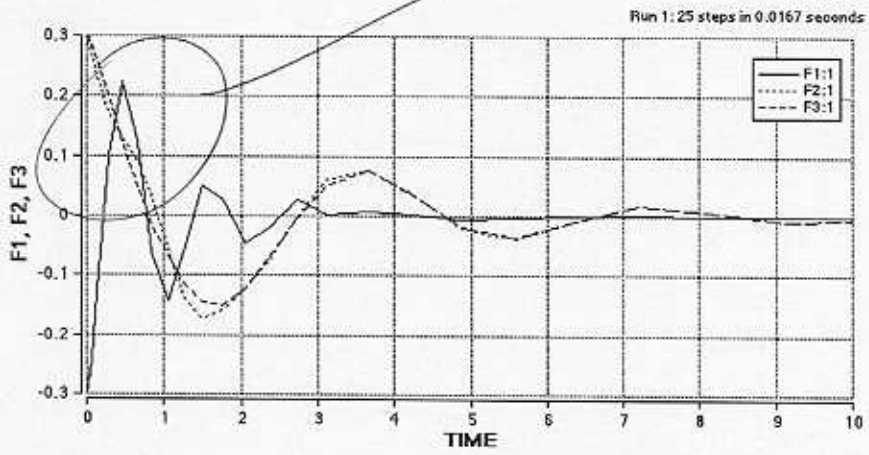

Fig. (4) Force and Time

In this experiment the values for c= 0.08, kl= 0.2, and ku= 3, X1= -1, X2= -1, X3= 0

Test 3

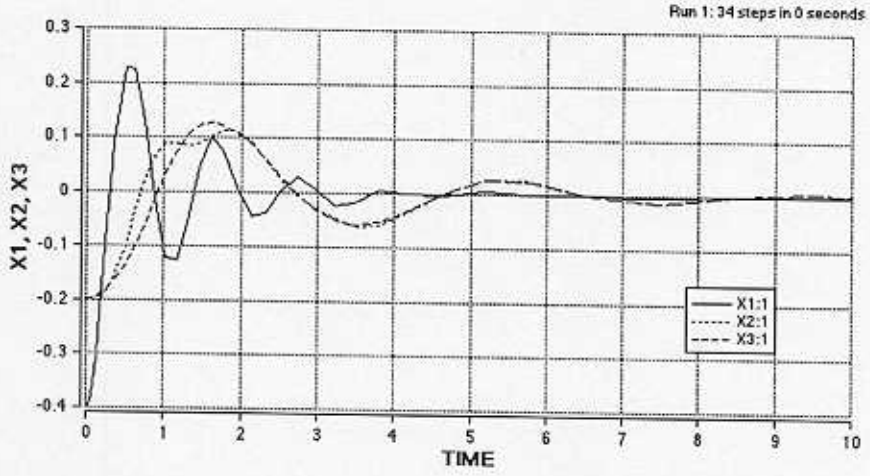

Fig (5) Displacement and Time

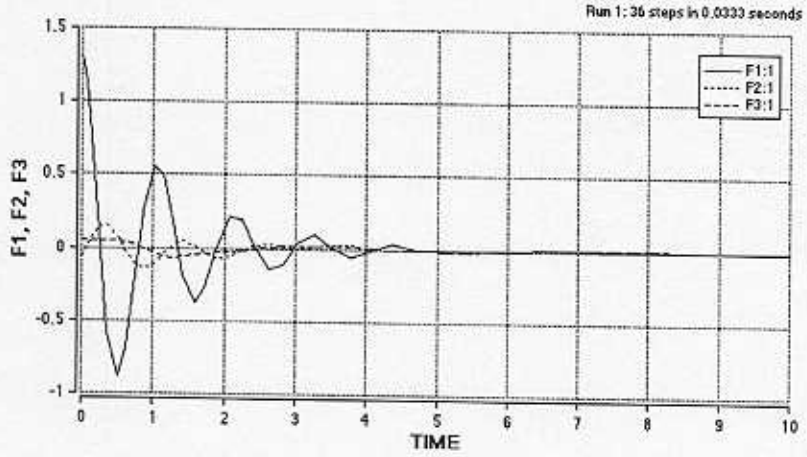

Fig. (6) Force and Time

The values for c=0.07, kl=0.2, and ku=3, X1=-0.2, X2=-0.2, and X3=-0.4

Test 4

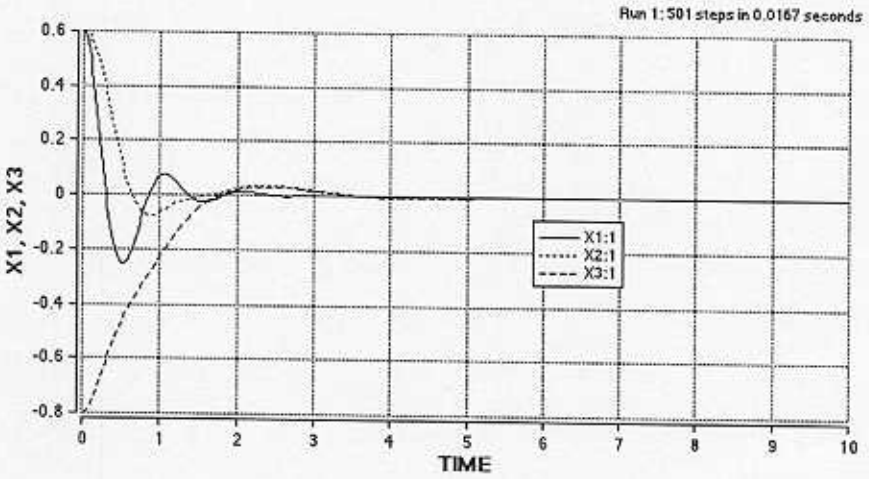

Fig (7) Relationship between Displacement and Time

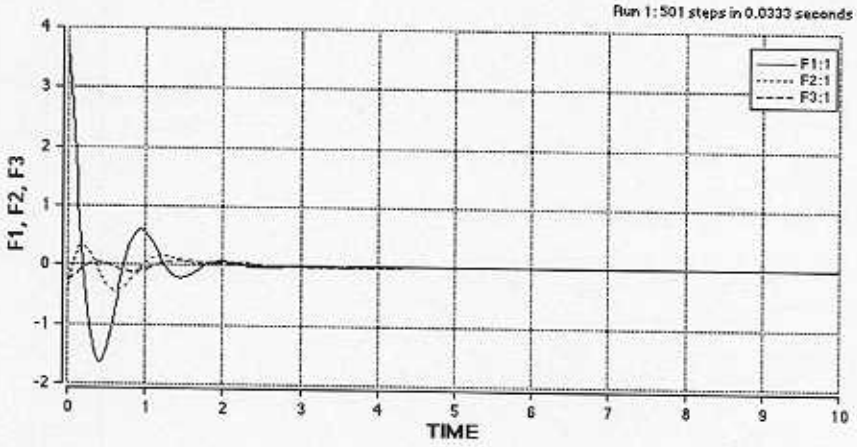

Fig (8) Relationship between Force and Time

The values for this test are c=0.2, kl=0.3, and ku=4, X1=-0.8, X2=0.6, and X3=0.6

Test 5

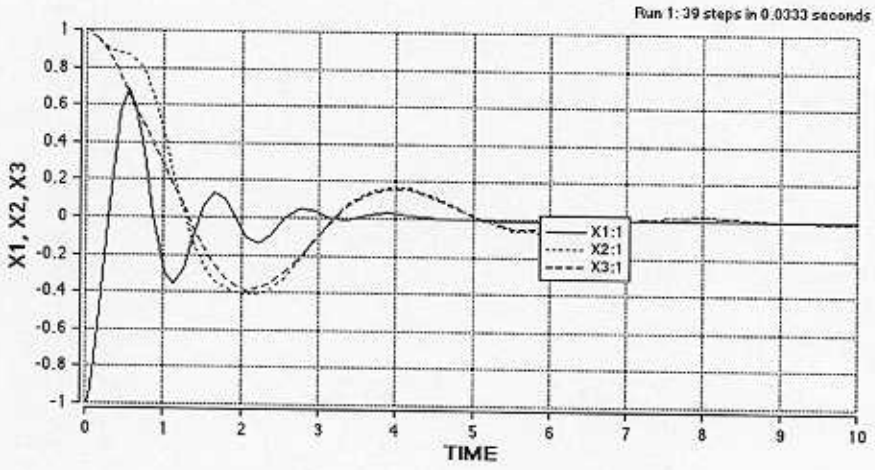

Fig (9) Shows the Relationship between Displacement and Time

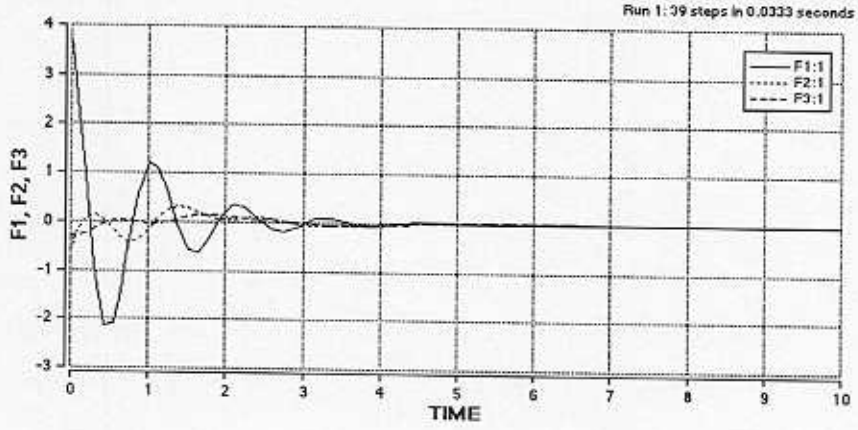

Fig (10) Relationship between Force and Time

The test values are c=0.1, kl=0.21, and ku=3, X1=-1, X2=1, and X3=1

Test 6

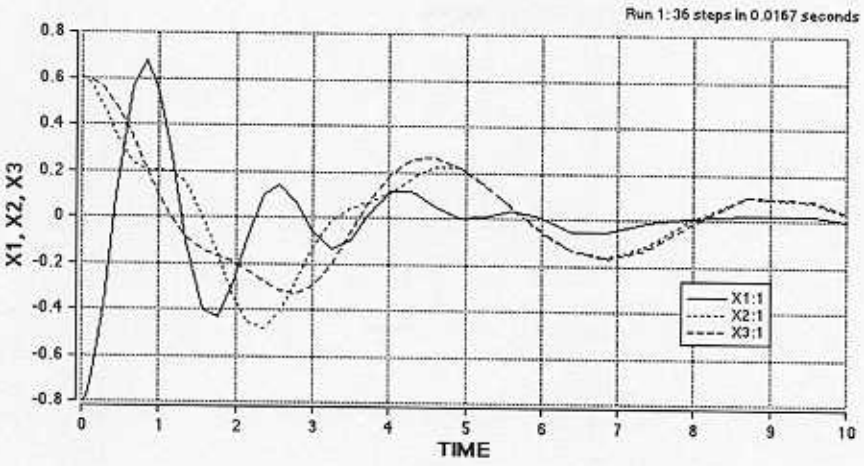

Fig (11) Relationship between the cell displacement and Time

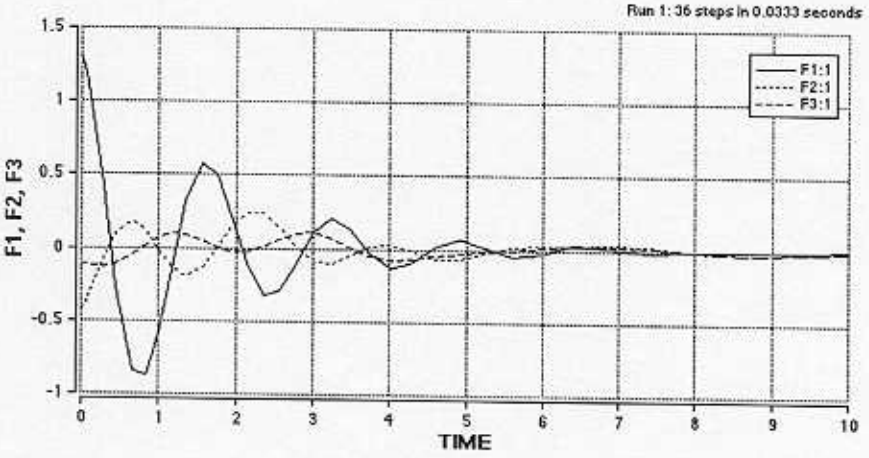

Fig (12) shows the Force generated in the cell and Time

Values for test 6 are c=0.04, kl=0.08 and ku=1, X1=-0.8, X2=0.6, X3=0.6

Test 7

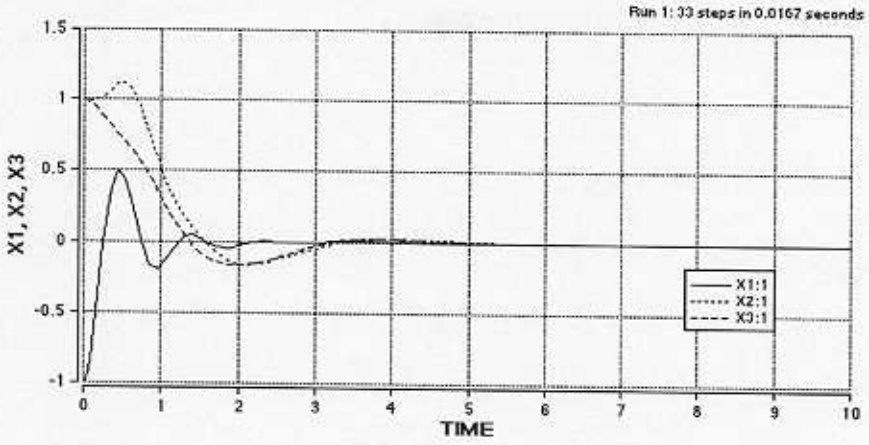

Fig (13) shows the change of the cells displacement with time

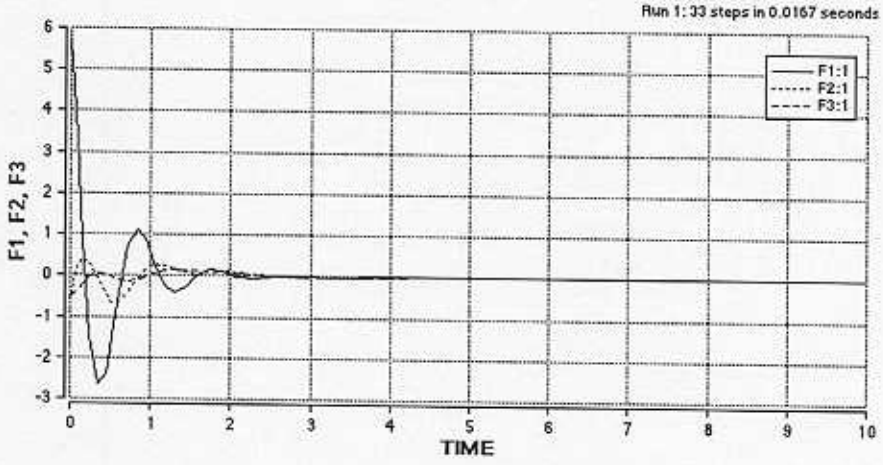

Fig (14) shows the force vs time

Test Values c=0.2, kl=0.4, and ku=5, X1=-1, X2=1, and X3=1

Summary

We have presented a simple model which relates basic cell biophysical properties to cell displacement, based on a chronological view of cell movement (cycle) of lamellipodal extension, cytoskeletal contraction, and relaxation.
To understand how variations in contractile force and cell rheology affect movement, experimental tests were run for different values of the mechanical properties C, kl, and ku and for different displacements X1, X2, X3.

By comparing the 7 previous graphs, we can conclude that the system reaches the steady state position with higher values of c in a faster time, comparing fig (13) for the displacement and fig (14) for the forces with the values of c=0.2, kl=0.4, ku=5 the system reaches its steady state position in 3 sec and 4 sec respectively, however the uropod takes a longer period of time to reach the equilibrium followed by the cell body and the lamellipod

For values of c=0, kl=0, and ku=0 the system was unstable which means the cell will not reaches its equilibrium at this stage.

References

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