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A mathematical model of the coupled mechanisms of cell adhesion, contraction and spreading

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Abstract Recen e ea ch ha ho n ha cell p eading i highl dependen on he con ac ili of i c o kele on and he mechanical p ope ie of he en i onmen i i loca ed in. The d namic of ch p oce i c i ical fo he de elopmen of i e enginee ing, a eg b i al o a ke pla e in o nd con ac ion, i e main enance and angiogene i . To be e nde and he nde l ing ph ic of ch phenomena, he pape de c ibe a ma hema ical fo m la ion of cell p eading and con ac ion ha co ple he p oce e of e be fo ma ion, p o ion g o h h o gh ac in pol me i a ion a he cell edge and d namic of c o -memb ane p o ein (in eg in) enabling cell- b a e a achmen . The e ol ing cell' c o kele on i modeled a a mi e of id, p o ein and lamen ha can e change ma and gene a e con ac ion. In pa ic la , be ide elf-a embling in o e be , ac in monome able o pol me i e in o an ac in me h o k a he cell' bo nda in o de o p h he memb ane fo a d and gene a e p o ion. The e p oce e a e po ible ia he de elopmen of cell- b a e a achmen comple e ha a i e f om he mechano- en i i e eq ilib i m of memb ane p o ein , kno n a in eg in . Af e de i ing he go e ning eq a ion d i ing he d namic of cell e ol ion and p eading, e in od ce a n me ical ol ion ba ed on he e ended ni e elemen me hod, combined i h a le el e fo m la ion. N me ical im la ion ho ha he p opo ed model i able o cap e he dependenc of cell p eading and con ac ion on b a e iffne and chemi . The e good ag eemen be een model p edic ion and e pe imen al ob e a ion gge ha mechanic pla a ong ole in o he co pled mechani m of con ac ion, adhe ion and p eading of adhe en cell .

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mechanism of stress fibre orientation with mechanical forces have been assessed by a variety of models, some based on purely thermodynamical arguments (Foucard and Vernerey 2012; Stamenović et al. 2009) and some based on biochemically arguments including signalling pathway (Civelekoglu-Scholey et al. 2005). At the cellular level, the development of global stress fibre organisation, contraction and adhesion have recently been the object of a formulation (Deshpande et al. 2008) based on empirical relationship describing the mechanically driven dissociation of stress fibres and integrin dynamics. A similar continuum approach was later introduced within the

Fig. 1 General configuration of an circular cell located on an elastic substrate with a representation of the three forms of actin considered in this study: globular, filamentous and bundled (stress fibers)

The actin cytoskeleton is a mixture of four major constituents representing the cytosol and actin in three different forms: globular, filamentous, and bundled (Fig. 1). In its globular form, actin easily diffuses through the cytoskeleton and thus, may be represented as a fluid phase in the present study. In its filamentous form, however, actin

$$\cdot \quad + \quad \left(\frac{V}{\quad} + \frac{V}{\quad} \right) + \quad \cdot + \left(\frac{\quad}{\quad} + \frac{\quad}{\quad} \right) = 0 \tag{7}$$

$$\left(\frac{V}{\quad} + \frac{V}{\quad} \right) + \quad \cdot + \left(\frac{\quad}{\quad} + \frac{\quad}{\quad} \right) + \left(\frac{\quad}{\quad} + \frac{\quad}{\quad} \right) = 0 \tag{8}$$

$$\cdot \quad + \quad \left(\frac{V}{\quad} + \frac{V}{\quad} \right) + \quad \cdot = 0 \tag{9}$$

$$\cdot \quad + \frac{1}{1 + \quad} \left(\quad \cdot \quad + \cdot \quad + \cdot \quad ^{F} \right) = 0 \tag{10}$$

he e **I** = 1 1 , i he c o ol p e , e, **T** he pa ial , e, in he pa i e c o kele on and $\mathbf{T}^F$ he pa ial , e, ind ced b , e, be . We no e he e ha he e m pa i e c o kele on– a ed on a b oad en e a i ep e en a n mbe of po ible componen con ib ing o he cell ela ici . Thi incl de fo in ance, mic o b le , in e media e lamen and he memb ane loca ed on op and he bo om of a plana cell. A ming mall defo ma ion (ain a e picall le han 10 % in he p oblem of in e e), a linea ela ic ela ion can be ed o de c ibe he pa i e c o kele on e pon e:

$$ = \frac{E}{1 \quad ^2}(\quad + \quad) + \frac{\quad}{1} \quad = \ , \quad \text{and} \quad = \ , \tag{13}$$

he e = 1 and = . The ma e ial pa ame e E and ep e en he Yo ng' mod l and Poi on' a io, e pec i el hile he adial and ci c mfe en ial linea ain and a e ela ed o he adial di placemen b = / and = / . A di c ed in mo e de ail in Ve ne e and Fa ad (2011), he pa ial , e, $\mathbf{T}^F$ of , e, be i p opo ional o he ol me f ac ion ^{F} and a i e f om o diffe en o ce : ac i e con ac ion and pa i e ela ic e pon e. We he efo e i e:

$$ ^F = \ ^F (E_1 \quad + \ ^*) \quad = \ , \tag{14}$$

he e he coef cien E_1 deno e he iffne of , e, be , hile he con ac ile , e, * i he e l of ac o-m o in c o -b idge d namic a he a come ic le el (Ve ne e and Fa ad 2011). Al ho gh a come e fo ce i kno n o depend on he a e of con ac ion a p edic ed b he Hill model (Hill 1938), e choo e o neglec hi a pec fo he p e en d and con ide ha he con ac ile , e, i con an and e al o ha fo nd in a a e of i ome ic con ac ion. Thi a mp ion i mo i a ed b he fac ha cell p eading i a lo p oce compa ed o he cha ac e i ic ime- cale of c o -b idge d namic and i he efo e in en i i e o he a e of elonga ion of a come e . Finall fo ce e ilib i m in he mi e follo f om he balance of linea momen m. Unde a i mme ic and plane- , e, condi ion , hi ield :

$$\frac{\quad}{\quad} + \frac{1}{\quad}(\quad \quad) \quad - = 0 \tag{15}$$

In abo e e a ion, deno e he hickne of he cell and ep e en he di ib ed ac ion fo ce on he memb ane a i ing f om he in e ac ion i h he nde l ing b- a e ia focal adhe ion. While hi fo ce i applied a he bo om of a cell h o gh i memb ane, i i e i alen o con ide i a a angen ial bod fo ce applied o he c o kele on b in oking plane , e, a mp ion . To nall cha ac e i e he beha - io of he nde l ing b a e, i i ef l o no e ha i hickne i all m ch la ge han ha of cell . In hi i a ion, , e, a ia ion a e e pec ed in a

m V

Fig. 3 In eg in ligand comple e : **a** ligand , lo af ni in eg in , and bo nd/ nbo nd high-af ni in eg in , **b** in eg in a e , **c** ela i e di placemen be een o ide of in eg in ligand comple

$$\mu \quad = \mu \tag{17}$$

a e ilib i m. A lo concen a ion, nbo nd lo af ni in eg in can picall be ie ed a a dil e ol ion in he id pho pho-lipid memb ane, ch ha hei chemical po en ial inc ea e i h hei a ea den i a follo :

$$\mu \quad = \mu_0 + \quad \ln\left(\frac{}{_0}\right) \tag{18}$$

he e μ_0 and $_0$ a e he f ee ene g and concen a ion of lo -af ni in eg in in anda d condi ion, e pec i el . The chemical abili of high af ni in eg in i kno n o depend on he amo n of en ile fo ce he a e bjec ed o (Sheme h e al. 2005; Pe ol e al. 2003; Tan e al. 2003). In o he o d , hen in eg in ph icall a ach o b a e ligand , cell con ac ion (f om e be) igge a e ching fo ce on he in eg in hich end o inc ea e hei abili . To cap e hi phenomenon, i i impo an o con ide he e i ence of high in ni in eg in in o condi ion : ho e hich a e bo nd (i h concen a ion) and ho e hich a e nbo nd (i h concen a ion) o b a e ligand . Follo ing La ffenb ge and Linde man (1993), he concen a ion of bo nd in eg in can be e p e ed a a f nc ion of he nde l ing ligand concen a ion a follo :

$$= \frac{}{1 + } \quad . \tag{19}$$

Thi e p e ion clea l ho ho inc ea ing he ligand concen a ion end o p omo e he a achmen of in eg in o he b a e. The abili a ion of in eg in i h e ch ha hen led o he follo ing fo m of hei chemical po en ial (De hpande e al. 2008):

$$\mu$$

he e μ_0

To characterize the membrane elasticity, it is useful to introduce the elastic potential $\Psi(E)$, such that the membrane stress reads:

$$\sigma = \frac{\partial \Psi}{\partial E} F \quad \text{and} \quad \Psi(E) = \sigma_0 E + \frac{1}{2} K (E)^2 \tag{29}$$

Here $F = \ell / \ell_0$ is the deformation gradient, σ_0 is the pre-existing surface tension and K is the stiffness of the cell membrane. The mechanical equilibrium of the membrane with cytoskeleton stresses is then given by the standard equation (Vernerey 2011; Vernerey and Farsad 2011):

$$\mathbf{T} \cdot \mathbf{n} = \nabla_s \cdot \mathbf{T} \quad \Longrightarrow \quad \sigma = \frac{\sigma_r}{\kappa} \tag{30}$$

where $\mathbf{T}$ is the stress tensor in the cytoskeleton, $\mathbf{n}$ is the outward normal to the cell, ∇_s is the surface gradient operator and $\mathbf{T} = \sigma \mathbf{e}$ is the surface tension vector. It can be shown that due to our axisymmetric assumptions, this equation reduces to the simple form shown in the right end side of (30) in which σ_r denotes the radial stress on the boundary.

2.3 Membrane protrusion and cell growth

Let us now concentrate on the phenomenon of membrane protrusion from a physical viewpoint. This aspect of cell mechanics is known to involve a strong interplay between actin polymerization at the cell's edge and membrane resistance (Cuvelier et al. 2007; DiMilla et al. 1991; Oster and Perelson 1985; Pollard and Borisy 2003; Vallotton et al. 2005; Wakatsuki et al. 2003; Xiong et al. 2010). Similar to the previous section, such chemo-mechanical coupling can be mathematically addressed by considering the chemical equilibrium of the cytoskeleton at the cell edge and how it is affected

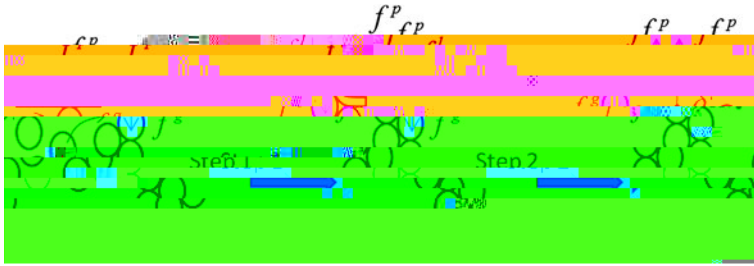

Fig. 4 A c cle of ac in pol me i a ion benea h he cell memb ane: **a** G-ac in monome in e be een

The o al change of f ee ene g d ing an en i e pol me i a ion c cle can hen be e ima ed b adding con ib ion f om ep 1 and 2. Thi ield :

$$\mu \quad = (\quad 2 \quad). \tag{34}$$

2. .2

We a e no in a po i ion o i e he chemical po en ial of ac in monome in hei agg ega ed fo m acco n ing fo he effec of memb ane and in eg in fo ce a follo (Hill 1981):

$$\mu \quad = \mu_0 + \quad \mu \quad = \mu_0 + \ (\quad 2 \quad) \tag{35}$$

No e ha he change in f ee ene g f om he p e ence of ph ical fo ce a added o he o iginal chemical po en ial μ_0, ince μ i in e p e ed a an ene g con med b he ac in c o kele on d ing a pol me i a ion ep. When he em i a e ili i m, he chemical po en ial of G-ac in and ac in lamen (agg ega ed ac in) a e e al ($\mu \quad = \mu$) and e ob ain:

$$\mu_0 + \ (\quad 2 \quad) = \mu_0 + \quad (\ ) \quad \text{i h} \quad = \text{——} \tag{36}$$

He e, e ed he fac ha he ol me f ac ion of ac in monome a e ilib i m i e al o / b e ing = 0 in (31

While he coef cien i gene all a f nc ion of he magni de of pa icipa ing fo ce (ee di c ion in Hill 1981), e con ide i he e a a con an ($= 1/2$) fo implici . In o he o d , e a me ha ph ical fo ce affec he on– and off– a e e all . U ing (39) and (31), i i hen po ible o ob ain he eloci of cell p eading (o he a e of ac in lamen g o h belo he memb ane) a :

$$= {}^{0} (\quad) \; \mathrm{e\ p} \left(\frac{(\quad 2 \quad)}{\quad} \right) \tag{41}$$

he e i he fo ce dependen concen a ion of G-ac in a e ilib i m de ned in (38). The abo e e a ion cap e man fea e of cell p eading. In pa ic la , one ee ha in (41) ha he memb ane e i ing fo ce end o dec ea e he a e of g o h hile he p lling fo ce inc ea e i . Since he in eg in p lling fo ce i di ec l ela ed o cell con ac ion, (41) cap e he co pling be een cell con ac ion and p eading: he mo e con ac ion, he fa e he p eading. F he mo e, he e a ion

Fig. 5 Rela ion hip be een he memb ane p o ion fo ce and and in eg in fo ce and mem-b ane en ion

p lling fo ce ma be ho gh of a he e l ing fo ce of di ib ed in eg in ac ion on a po ion of he cell edge ho e leng h i he a e aged di ance be een o ad ancing ac in lamen . Thi leng h can hen be calc la ed f om he ac in ol me f ac ion a he cell edge b $= 4 /$ (Fig. 5). Thi lead o he e ima ion of he p lling fo ce a :

$$= \frac{1}{2} \qquad = \frac{2}{} \tag{44}$$

he e i he in eg in fo ce a he cell pe ime e and he p od c i he effec i e a ea on hich he in eg in ac ion help he pol me i a ion of a ingle lamen . No e ha (43) and (44) p o ide a clea ela ion hip be een he mechanic of in eg in , he memb ane e and he a e of cell g o h in (41).

he cell memb ane i gi en in e m of he in eg in f ac ion and and nall he defo ma ion of he b a e i en i el kno n ia he kno ledge of i adial di placemen . The abo e eigh a iable ma be de e mined h o gh he follo ing eigh e a ion de i ed in he p e io ec ion:

Chemical equilibrium

$$\text{S e } \text{ be} \qquad \mu = \mu^{F} \text{ in} \tag{45}$$

$$\text{Ac in lamen} \qquad \mu = \mu \text{ on} \tag{46}$$

$$\text{Cell memb ane} \qquad \mu = \mu \text{ in} \tag{47}$$

Mass conservation

$$\text{C o ol} \qquad \dot{} + \left(\frac{v}{} + \frac{v}{} \right) + \dot{} + \left(\frac{}{} + \frac{}{} \right) = 0 \tag{48}$$

$$\text{Mi e} \qquad \left(\frac{v}{} + \frac{v}{} \right) + \dot{} + \left(\frac{}{} + \frac{}{} \right) + \left(\frac{}{} + \frac{}{} \right) = 0 \tag{49}$$

$$\text{In eg in} \qquad \frac{(+)}{} + (+) \left(\frac{v}{} + \frac{v}{} \right) + \left(\frac{}{} + \frac{}{} \right) = 0 \tag{50}$$

Mechanical equilibrium

$$\text{Cell} \qquad \frac{}{} + \frac{1}{}(\quad) + \frac{F}{} + \frac{1}{}(F \quad F) - \quad = 0 \tag{51}$$

$$\text{S b a e} \qquad \frac{}{} + \frac{(\quad)}{} + \quad = 0 \tag{52}$$

The e e a ion a e complemen ed b he e bo nda condi ion (co e ponding o he abo e diffe en ial e a ion) and ini ial condi ion , pecif ing he a e of he cell a he beginning of he im la ion . The e condi ion a e ch ha he cell and b a e a e ini iall ndefo med and np e i ed:

$$(,0) = 0 \qquad (,0) = 0 \qquad (,0) = 0 \tag{53}$$

In addi ion, i i a med ha he compo i ion of he cell con i of 25 % ol me f ac ion of elemen comp i ing he pa i e c o kele on, 5 % ol me f ac ion of ac in monome and no ini ial e be (efe ence fo he e n mbe a e gi en in Table 1).

$$(,0) = 0.25 \qquad (,0) = 0.05 \qquad ^{F}(,0) = 0 \tag{54}$$

and all in eg in a e o iginall in hei lo af ni a e (ee Table 1 fo efe ence):

$$(,0) = 5 \quad ^{15} \qquad (,0) = 0 \tag{55}$$

Conce ning he bo nda condi ion , e a me ha he e a e no e of c o ol and ac in monome ac o he cell memb ane and no lo af ni in eg in a e allo ed o en e he em. In oking E . (11) and (26), e can i e:

Table 1 Pa ame e u ed in he im la ion

De ni ion	S mbol	Val e	Uni	Refe ence
C o ol ol me f ac ion				

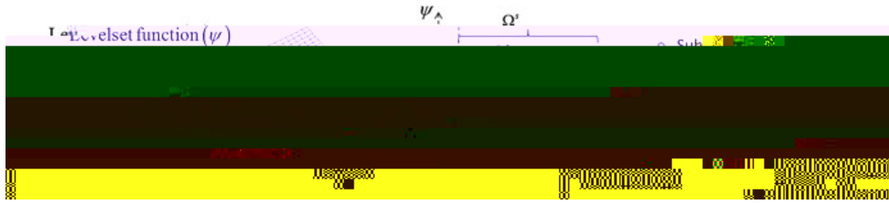

Fig. 6 Illustration of the level set function describing the cell boundary and the degrees of freedom associated with nodes in the computational domain

where the quantity is defined as the tensile stress in the membrane. Finally, the above system of equations is coupled with the growth equation (41) in order to determine the motion of the cell boundary in time. The numerical approach to solve (48–52) is discussed below.

3.1 Cell-substrate equilibrium

In order to determine the spatial and time evolution of the various continuum fields, the physical domains (representing cell and substrate) must be discretized in a finite number of elements and nodes. A potential issue with the present problem is that cell

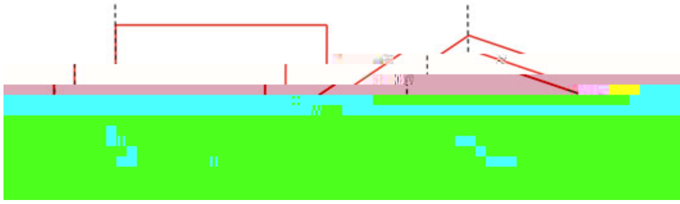

Fig. 7 a

He e = 1, 2, 3 deno e he local node n mbe fo each elemen and he e m $\bar{\mathbf{u}}$ and $\bar{\bar{\mathbf{u}}}$ co e pond o ong and eak deg ee of f eedom ha ani h fo non-en iched elemen . S b i ing he fini e in e pola ion (58) in he eak fo m and linea i ing he eq a ion , one can ho ha he p oblem ed ce o ol ing he follo ing algeb aic i e a i e p oblem:

$$\mathbf{C}\dot{\mathbf{U}} + \mathbf{K} \ \mathbf{U} + \mathbf{F} = \mathbf{0} \tag{63}$$

he e **U** deno e he ec o con aining global deg ee of f eedom, hile **C**, **K** and **F** a e he damping ma i , iffne ma i and fo ce ec o , e pec i el (ee Appendi A.2 fo a mo e de ailed e plana ion). Eq a ion (63) i ol ed a each ime ep ing a Ne on-Raph on p oced e and a back a d E le in eg a ion me hod i ed o comp e he nkno n field a each ime ep a follo :

$$\mathbf{U} = \ \dot{\mathbf{U}} \cdot \tag{64}$$

he e deno e he ime inc emen . Upon ob aining a ol ion a ime inc emen , he me hod con i of comp ing he a e $\dot{\mathbf{U}}$ a he ne ime ep +

$$\dot{\mathbf{U}} \ (+ \ ) = \dot{\mathbf{U}} \ ^{1}(+ \ ) + \ \dot{\mathbf{U}} \tag{65}$$

he e he al e $\dot{\mathbf{U}}$ i comp ed fo each i e a ion b b i ing Eq . (64) and (65) in o Eq. (63). Thi lead o he follo ing eq a ion:

$$\left(\mathbf{C} \ _{+}^{1} \ + \ \ \mathbf{K} \ _{+}^{1}\right) \cdot \dot{\mathbf{U}} \ = \ \left(\mathbf{F} \ _{+}^{1} \ + \mathbf{C} \ _{+}^{1} \ \cdot \dot{\mathbf{U}} \ _{+}^{1}\right) \cdot \tag{66}$$

I e a ion a e hen epea ed n il he no m of he ec o **U** i malle han a mall ole ance.

3.2 Cell g o h and le el e ol ion

To model cell g o h, e l f om he eq ilib i m eq a ion a each ime- ep can be ed o e ima e he p lling and memb ane e i ance fo ce appea ing in (41). Since he cell adi i defined in e m of he le el e f nc ion , i a e of change in ime can impl be e p e ed in e m of he adi ional le el e ol ion eq a ion (D dd e al. 2008):

$$— = — + \ — = 0 \tag{67}$$

he e i cell bo nda eloci comp ed in (41). Defining he le el e a a ign-di ance f nc ion (i.e. — = 1), e can find he e p e ion of he le el e f nc ion a ime ep + a :

$$^{+} \ = \ + \ \cdot \ . \tag{68}$$

Growth typically involves the creation of new material points, whose composition is unknown, at the cell boundary. It is thus necessary to make some assumptions regarding the state of the mixture at the new cell edge in terms of the constituents' volume fractions. To ensure the continuity of both a continuum field and its derivatives during cell growth, a realistic assumption (Ateshian 2007) consists of approximating a field

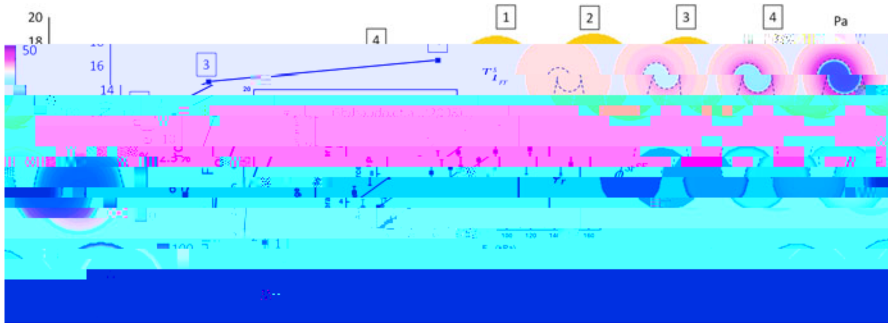

Fig. 8 Rela ion hip be een cell con ac ion and cell a ea fo diffe en b a e iffne . The model p edic a nonlinea ela ion hip be een con ac ion and b a e iffne in ag eemen i h e pe imen on mic opilla (Ghiba do e al. 2008). Fo compa i on p po e , he im la ed fo ce in he o dina e i e al o he o al comp ed in eg in fo ce di ided b he n mbe of pilla f om e pe imen al image and m l iplied b he a io of cell a ea ob ained f om e pe imen and im la ion . The e ol ion of adial e in he b a e, ol me f ac ion F of e be in he adial di ec ion and he concen a ion of high af ni in eg in a e al o ho n fo diffe en b a e iffne

Fig. 9 E ol ion of p lling fo ce, memb ane e i ance fo ce and cell a ea in ime

C Cell adhe ion i p o ided b he cl e ing of in eg in ligand comple e l ing f om he chemical e ilib i m de c ibed in Sec . 2.2. Cell con ac ion igge a adial epa a ion be een i memb ane and he nde l ing b a e, ch ha he epa a ion eache a ma im m a he cell pe iphe . When ligand a e p e en , he in eg in e i ing hi epa a ion a e bjec ed o la ge e ching fo ce in hi egion, hich lead o hei abili a ion [acco ding o (22)]. Thi e plain he acc m la ion

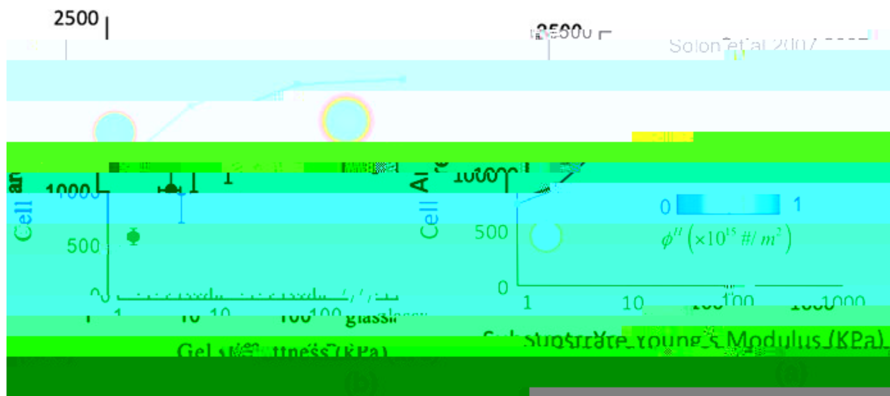

Fig. 10 Change of cell a ea and high-af ni in eg in concen a ion a ead a e fo diffe en b a e iffne , and compa i on i h e pe imen al e l of Solon e al. (2007)

he e he p eading a e, p lling fo ce and memb ane e i ing fo ce a e depic ed a a f nc ion of ime. I i een ha he p eading a e i a f nc ion of he diffe ence be een and ch ha hen ani he (he o c e mee), he eloci of p eading become q a i-negligible. Ano he effec of he p lling fo ce i o inc ea e he a e of p eading b ai ing he ac i a ion ene g . The model he efo e p edic a i e in bo h cell a ea and p eading a e i h con ac ion and b a e iffne a ho n b he fac ha he cell a ea become la ge a one mo e o he igh in Fig. 8.

The model pa ic la l p edic ha he h ee abo e mechani m a e ongl in e ela ed and dependen on b a e iffne and ligand den i . We ne a e he o ndne of he model b compa ing n me ical p edic ion and e pe imen al mea - emen f om he li e a e.

4.2 Effec of b a e iffne on cell a ea

E pe imen al die on b obla ha e ho n ha cell a ea (Solon e al. 2007) inc ea e i h b a e iffne in a nonlinea fa hion (Fig. 10). He e, e in e i- ga e hi dependenc b con ide ing an ela ic b a e ho e ligand concen a ion i in ni el la ge ($\to \infty$) o en e ha cell p eading i onl affec ed b iffne . To in e iga e cell p eading, e a f om an o iginal cell con g a ion of face a ea $A_0 \approx 600\mu$ ^{2} in hich no e , be and high af ni in eg in a e p e en . Since hi em i o iginall o of e ilib i m, e ob e e a ime dependen e , be fo ma ion, in eg in ligand adhe ion and cell p eading ha e en all eache a

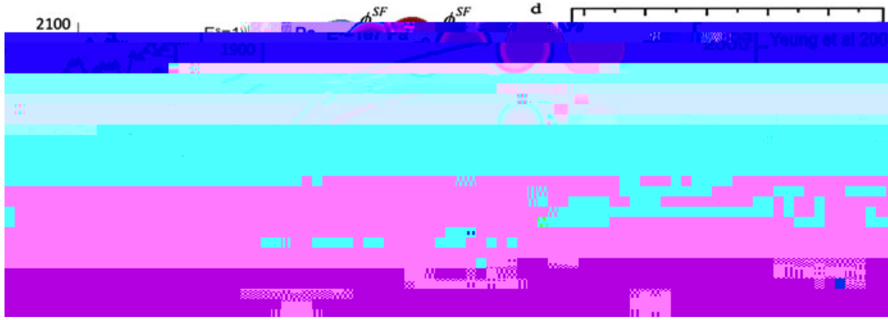

Fig. 11 **a** Change of cell a ea and e be ol me f ac ion d ing g o h fo diffe en b a e iffne , and **b** e pe imen al e l of Ye ng e al. (2005)

a limi , hich depend on o mechani m ha ac again ac in pol me i a ion. Fi , e be e en all each a ma im m concen a ion, hich limi he con ac ion a cell can e e on i o nding and h he p lling fo ce. Second, acco ding o (41), he a e of p eading i con olled b he compe i ion be e4b3l80 e 53.406082p lling and he e i ing fo ce. A ob e ed in Fig. 9, he e i ing fo ce, hile o iginall eak, inc ea e a a m ch fa e a e han he p lling fo ce and e en all become he dominating fac o ; hi p an end o cell p eading.

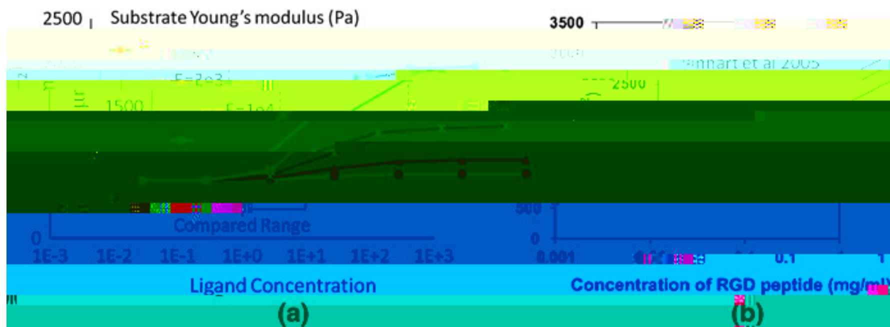

Fig. 12 Change of cell a ea a ead a e fo diffe en ligand concen a ion, and compa i on i h e pe imen al e l of Reinha -King e al. (2005)

ha cell a ea a a linea f nc ion of ligand den i i hin concen a ion ha anged f om 0.001 o 1 mg/ml. To kno he he he p opo ed model co ld ep od ce hi end, e con ide ed a cell l ing on a b a e of gi en iffne and a ied he ligand concen a ion f om 0.001 o 1,000 ligand/μm^2. A depic ed in Fig. 12, he model p edic a nonlinea ela ion hip be een ligand den i and cell a ea. While hi e l ma eem con adic o i h e pe imen al end , he e a e e e al e plana ion fo he ob e ed di c epanc . Fi , i ho ld be no ed ha he ange of ligand concen a ion con ide ed in he im la ion i m ch g ea e han ha in e iga ed e pe i men all . In fac , if one compa e end i hin he ame concen a ion ange, he p edic ed inc ea e in cell a ea i e clo e o he linea ela ion hip een in e pe i men . F he mo e, o ide of hi ange, model p edic ion a e pe fec l o nd a i i kno n ha cell a ea canno con in o l inc ea e and m each a ma im m, ega dle of he concen a ion of ligand. Simila l , hen no ligand a e p e en , cell a ea m con e ge o a mall b ni e al e. Thi j i e he fac ha cell a ea ha ho i on al a mp o e a ligand den i end o e o and in ni . Finall he inc ea e of cell a ea i h ligand concen a ion can be e plained on he ba i of (22). On he one hand, hen ligand den i ani he , in eg in canno a ach o he b a e; hi p ecl de he e i ence of a p lling fo ce and he a ocia ed inc ea e in cell a ea. On he o he hand, hen ligand den i i high, cell can a ach o he b a e and gene a e con ac ion; hi p od ce ea alan ,an , o c ,a

ligand attachment on the plasma membrane is promoted by large integrin pulling force and tends to reinforce both contraction and adhesion on stiff substrates. Finally, the phenomenon of protrusion growth is the result of an interplay between two opposite forces: the integrin pulling force at the edge of the cell and the stretching and bending-resistance of the cell membrane. These mechanisms have been presented within a thermodynamically consistent framework that obeys fundamental principles such as

and enfo cing he fac ha $\dot{}_{yy} =$, e ob ain he follo ing e p e ion fo $_{yy}$:

$$_{yy} = \frac{1}{1} \; \frac{}{\bar{E}}(1 +)(1 \quad 2) \quad (\quad + \quad) \Big] \tag{71}$$

he e $\bar{E}$ and a e he Yo ng mod l and Poi on a io of he ac in lamen ne o k. Thei ela ion hip i h Lame con an appea ing in (70) i gi en belo :

$$\bar{E} = \frac{\mu'(3 \quad + 2\mu')}{\quad + \mu'}; \quad \text{and} \quad = \frac{}{2(\quad + \mu')} \tag{72}$$

We no i h o e p e he di e gence $\cdot \mathbf{v}$ of he eloci eld $\mathbf{v}$ fo b i ion in he e a ion of ma balance (4 6). Fo a h ee dimen ional p oblem, he di e gence ead $\cdot \mathbf{v} = \dot{} + \dot{} + \dot{}_{yy}$ he e a pe impo ed do i ed o deno e a ime de i a i e. U ing he fac ha :

$$\dot{}_{yy} = \frac{1}{1} \Big[\frac{\dot{}}{\bar{E}}(1 +)(1 \quad 2) \quad (\dot{} \quad + \dot{} \quad) \Big] \tag{73}$$

f om (71), e can e i e:

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