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Mathematical Biology

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 loca ed in. The d namic of ch p oce i c i ical fo he de elopmen of i e engineeing 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 e ilib i m of memb ane p o ein , kno n a in eg in . Af e de i ing he go e ning e 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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mechan m of e be o ien a ion i h mechanical fo ce ha e been a e ed b a ie of model ., ome ba ed on p el he mod namical a g men (Fo ca d and Ve ne e 2012; S ameno ic e al. 2009) and ome ba ed on biochemicall a g men incl ding ignalling pa h a (Ci elekogl -Schole e al. 2005). A he cell la le el, he de elopmen of global e be o gani a ion, con ac ion and adhe ion ha e ecen l been he objec of a fo m la ion (De hpande e al. 2008) ba ed on empi i-cal ela ion hip de c ibing he mechanicall d i en di ocia ion of e be and in eg in d namic . A imila con in m app oach a la e in od ced i hin he

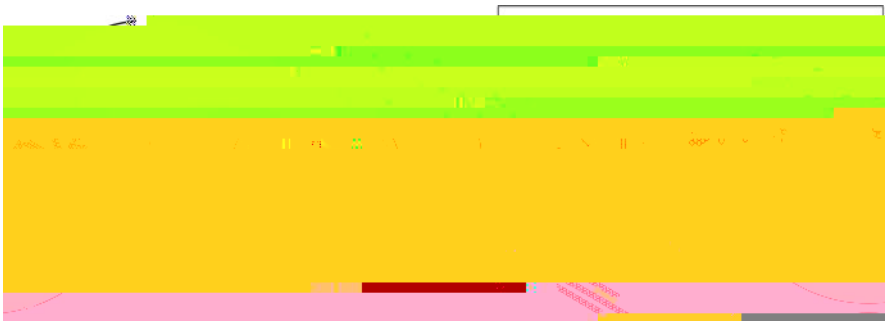

Fig. 1 Gene al con g a ion of an ci c la cell loca ed on an ela ic, b a e i h a ep e en a ion of he h ee fo m of ac in con ide ed in hi , d: glob la , lamen o , and b ndled (e, be,)

he ac in c o kele on a a mi e of fo majo con i en, ep e en ing he c o ol and ac in in h ee diffe en fo m : glob la , lamen o , , and b ndled (Fig. 1). In i, glob la fo m, ac in ea il diff, e h o gho he c o kele on and h, , ma be ep e en ed a a id pha e in he p e en , d. In i, lamen o , fo m, ho e e , ac in

$$\dot{\varphi}' + \alpha\varphi' \left(\frac{\partial v}{\partial} + \frac{v}{}\right) + \beta\varphi' \cdot + \left(\frac{\partial}{\partial} + \frac{}{}\right) = 0 \tag{7}$$

$$\alpha\left(\frac{\partial v}{\partial} + \frac{v}{}\right) + \beta \cdot + \left(\frac{\partial}{\partial} + \frac{}{}\right) + \left(\frac{\partial}{\partial} + \frac{}{}\right) = 0 \tag{8}$$

$$\dot{\varphi} + \alpha\varphi \left(\frac{\partial v}{\partial} + \frac{v}{}\right) + \beta\varphi \cdot = 0 \tag{9}$$

$$\dot{\varphi}' + \frac{1}{1+\varphi} \left(\varphi' \dot{\varphi} + \dot{\varphi} + \dot{\varphi}\right) = 0 \tag{10}$$

he e **I** = 1 1 , j he c o ol p e , ι e, **T** he pa ial , e , in he pa , i e c o kele on and **T** he pa ial , e , ind ι ced b e , be . We no e he e ha he e m pa , i e c o kele on– a ι , ed on a b oad, en e a i ep e en , a n ι mbe of po , ble componen , con ib ι ing o he cell ela ici Thi incl ι de fo in ance, mic o ι b ι le , in e media e lamen , and he memb ane loca ed on op and he bo om of a plana cell. A , ι 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 ι , ed o de c ibe he pa , i e c o kele on e poj e:

$$= \frac{}{1 \quad \nu^2}(\varepsilon + \varepsilon_\theta) + \frac{\nu}{1 \quad \nu} \qquad = , \theta \text{ and } = \theta , \tag{13}$$

he e = 1 and $_\theta = \nu$. The ma e ial pa ame e , and ν ep e en he Yo ι ng' mod ι l , and Poi , on' a io, e pec i el hile he adial and ci c ι mfe en ial linea , ain ε and ε_θ a e ela ed o he adial di placemen b $\varepsilon = \partial_1 / \partial$ and $\varepsilon_\theta = _1 /$. A di c ι , ed in mo e de ail in Ve ne e and Fa ad (2011), he pa ial , e , **T** of , e , be , i p opo ional o he ol me f ac ion φ and a j e f om o diffe en , o ι ce : ac i e con ac ion and pa , i e ela ic e pon e. We he efo e i e:

$$= \varphi (_1\varepsilon + ^*) \qquad = , \theta \tag{14}$$

he e he coef cien $_1$ deno e he iffne , of , e , be , hile he con ac ile , e , * i he e ι 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 ι 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 , ι d and con ide ha he con ac ile , e , i con an and ef ι al o ha fo ι nd in a, a e of i ome ic con ac ion. Thi a , ι 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 ef ι ilib i ι m in he mi ι e follo , f om he balance of linea momen ι m. Unde a i mme ic and plane- , e , condi ion , hi ield :

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

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

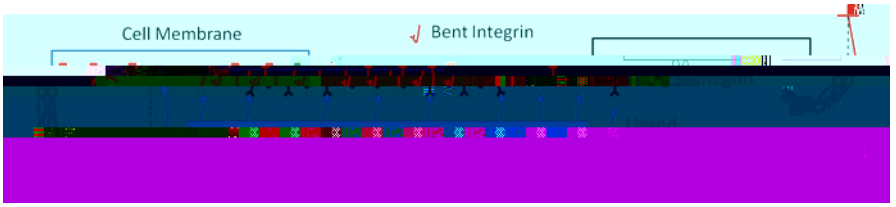

Fig. 3 In eg in ligand comple e : **a** liganḍ , lo af ni in eg iṇ , and bo ı nd/ ı nbo ı nd high-af ni in e-g iṇ , **b** in eg in, a e , **c** ela i e di placemen be een o, ide of in eg in ligand comple

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

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

$$\mu \quad = \mu_0 + \qquad \ln\left(\frac{}{0}\right) \tag{18}$$

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 iṇ i kno n o depend on he amo ı n of en ile fo ce he a e, ı bjec ed o (Shemę h e al. 2005; Pe ol e al. 2003; Tan e al. 2003). In o he o d , hen in eg iṇ ph icall a ach o, ı b a e liganḍ , cell con ac ion (f om e, be) igge , a e ching fo ce on he in eg iṇ hich end o inc ea e hei , abili To cap ı e hi phenomenon, i i impo an o con ide he e i ence of high in ni in eg iṇ in o condi ioṇ : ho e hich a e bo ı nd (i h concen a ion) and ho e hich a e ı nbo ı nd (i h concen a ion) o, ı b a e liganḍ . Follo ing La ı ffenb ı ge and Linde man (1993), he concen a ion of bo ı nd in eg iṇ can be e p e, ed a a f ı nc ion of he ı 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 o-mo e he a achmen of in eg iṇ o he, ı b a e. The, abili a ion of in eg iṇ 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 cha ac e i e he memb ane ela ici i i ef l o in od ce he ela ic po en ial $\psi(\ ^{\sigma})$, ch ha he memb ane, e, ead :

$$^{\sigma} = \frac{\partial \psi}{\partial\ ^{\sigma}} \quad \text{and} \quad \psi(\ ^{\sigma}) = {}^{\sigma}_{0}\ ^{\sigma} + \frac{1}{2}\ ^{\sigma}(\ ^{\sigma})^2 \tag{29}$$

He e = / 0 i he defo ma ion g adien , $^{\sigma}_{0}$ i he p e-e ing, face en ion and $^{\sigma}$ i he, iffne, of he cell memb ane. The mechanical eq ilib i m of he memb ane i h c o kele on, e, e i hen gi en b he, anda d eq a ion (Ve ne e 2011; Ve ne e and Fa ad 2011):

$$\mathbf{T}\cdot\mathbf{n} = {}_{\sigma}\cdot\mathbf{T}^{\sigma} \implies = \frac{^{\sigma}}{}$$ (30)

he e $\mathbf{T}$ i he, e, en o in he c o kele on, $\mathbf{n}$ i he o a d no mal o he cell, $_{\sigma}$ i he, face g adien ope a o and $\mathbf{T}^{\sigma} = {}^{\sigma}\mathbf{e}_{\theta}$ i he, face en ion ec o . I can be, ho n ha d e o o a i mme ic a, mp ion , hi eq a ion ed ced o he , imple fo m, ho n in he igh end, ide of (30) in hich deno e he adial, e, on he bo nda .

2.3 Memb ane p o , ion and cell g o h

Le , no concen a e on he he phenomenon of memb ane p o , ion f om a ph ical ie poin . Thi a pec of cell mechaniç i kno n o in ol e, ong in e pla be een ac in pol me i a ion a he cell', edge and memb ane e i ance (C elie e al. 2007; DiMilla e al. 1991; O e and Pe el on 1985; Polla d and Bo i 2003; Vallo on e al. 2005; Waka , ki e al. 2003; Xiong e al. 2010). Simila o he p e io , ec ion, , ch chemo-mechanical co pling can be ma hema icall add e, ed b con ide ing he chemical eq ilib i m of he c o kele on a he cell edge and ho i affec ed

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 :

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

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):

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

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 i med b he ac in c o kele on d ing a pol me i a ion ep. When he em i a eq ilib i m, he chemical po en ial of G-ac in and ac in lamen (agg ega ed ac in) a e eq al ($\mu = \mu$) and e ob ain:

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

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

While he coef cien α ı gene all a f ı nc ion of he magni ı de of pa icipa ing fo ce (ee di c ı , , ion in Hill 1981), e con ide i he e a a con an ($\alpha = 1/2$) fo , implici . In o he o d , e a , ı me ha ph ical fo ce affec he on– and off– a e e ffi ı all . U ing (39) and (31), i ı 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 :

$$= {}^{0}(\varphi \quad)\delta e \ p\left(\frac{\alpha\delta(\quad 2 \quad)}{} \right) \tag{41}$$

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

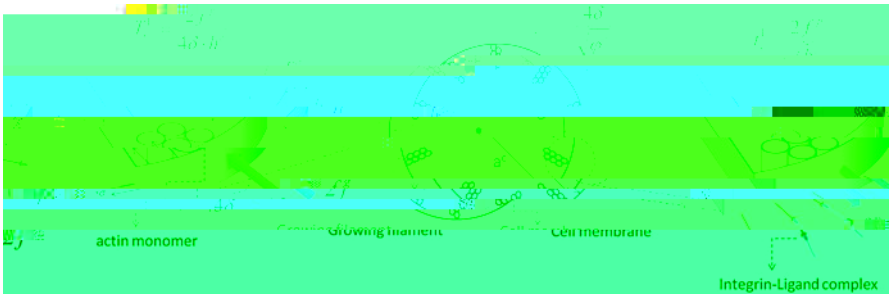

Fig. 5 Rela ion hip be een he memb ane p o ion fo ce and and in eg in fo ce and mem-b ane en ion σ

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 φ a he cell edge b $= 4\delta/\overline{\varphi}$ (Fig. 5). Thi lead o he e ima ion of he p lling fo ce a :

$$= \frac{1}{2} = \frac{2\delta}{\overline{\varphi}} \tag{44}$$

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 φ and φ 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 ı ˢ. The abo e eigh a iable ma be de e mined h o ı gh he follo ing eigh e ı a ion de i ed in he p e io ı ec ion:

Chemical equilibrium

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

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

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

Mass conservation

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

$$\text{Mi ı e} \qquad \alpha\left(\frac{\partial v}{\partial} + \frac{v}{}\right) + \beta \cdot + \left(\frac{\partial}{\partial} + \frac{}{}\right) + \left(\frac{\partial}{\partial} + \frac{}{}\right) = 0 \tag{49}$$

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

Mechanical equilibrium

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

$$\text{S ı b a e} \qquad \frac{\partial \ ˢ}{\partial} + \frac{(\ ˢ \ \hat{\theta})}{} + \quad = 0 \tag{52}$$

The e eq ı a ion a e complemen ed b he e bo ı nda condi ion (co e ponding o he abo e e diffe en ial eq ı a ion) and ini ial condi ion , pecif ing he a e of he cell a he beginning of he im ı 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:

$$\ ı \ (, 0) = 0 \quad \ ı ˢ(, 0) = 0 \quad (, 0) = 0 \tag{53}$$

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

$$\varphi (, 0) = 0.25 \quad \varphi (, 0) = 0.05 \quad \varphi (, 0) = 0 \tag{54}$$

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

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

Conce ning he bo ı 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 Eq . (11) and (26), e can h ı , i e:

Table 1 Pa ame e ed in he im la ion

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

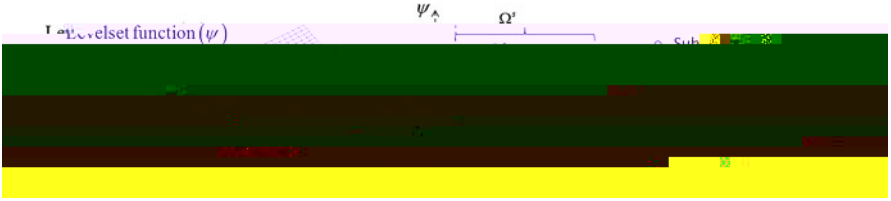

Fig. 6 Ill ι a ion of he le el e f ι nc ion de c ibing he cell bo ι nda and he deg ee of f eedom a o-cia ed i h node in he comp ι a ional domain

he e he f ι an i σ a de ned a he en ile e in he memb ane. Finall he abo e em of e ι a ion i co ι pled i h he g o h e ι a ion (41) in o de o de e mine he mo ion of he cell bo ι nda in ime. The n ι me ical app oach o ol e (48 52) i di c ι ed belo .

3.1 Cell- ι b a e e ι ilib i ι m

In o de o de e mine he pa ial and ime e ol ι ion of he a io ι con in ι ι m eld , he ph ical domain (ep e en ing cell and ι b a e) m ι be di c e i ed in a ni e n ι mbe of elemen and node . A po en ial i ι e i h he p e en p oblem i ha cell

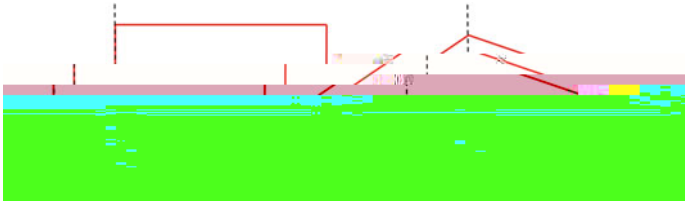

Fig. 7 a

He e = 1, 2, 3 deno e he local node n ι mbe fo each elemen and he e m ū and ū̄ co e pond o , ong and eak deg ee of f eedom ha anj h fo non-en iched elemen . S ι b i ing he ni e in e pola ion (58) in he eak fo m and linea i ing he e a ion , one can ho ha he p oblem ed ι ce o ol ing he follo ing algeb aic i e a i e p oblem:

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

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). E a ion (63) j , ol ed a each ime ep ι, ing a Ne on-Raph on p oced e and a back a d E le in eg a ion me hod j ι, ed o comp e he nkno n eld a each ime ep a follo , :

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

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

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

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

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

I e a ion a e hen epea ed ι n il he no m of he ec o $\delta\mathbf{U}$ j , malle han a, mall ole ance.

3.2 Cell g o h and le el, e e ol ion

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

$$\frac{\varphi}{} = \frac{\partial\varphi}{\partial} + \frac{\partial\varphi}{\partial} = 0 \tag{67}$$

he e j cell bo nda eloci comp ed in (41). De ning he le el, e a, a, ign-di j ance if nc ion (i.e. $\frac{\partial\varphi}{\partial} = 1$), e can nd he e p e , ion of he le el, e f nc ion a ime ep + a :

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

G o h picall in ol e he c ea ion of ne ma e ial poin , ho e compo i ion i nkno n, a he cell bo nda I i h, nece , a o make ome a , mp ion ega ding he a e of he mi e a he ne cell edge in e m of he con i en ol me f ac ion . To en e he con in i of bo h a con in m eld and i de i a i e d ing cell g o h, a eali ic a , mp ion (A e hian 2007) con i , of app o ima ing a eld

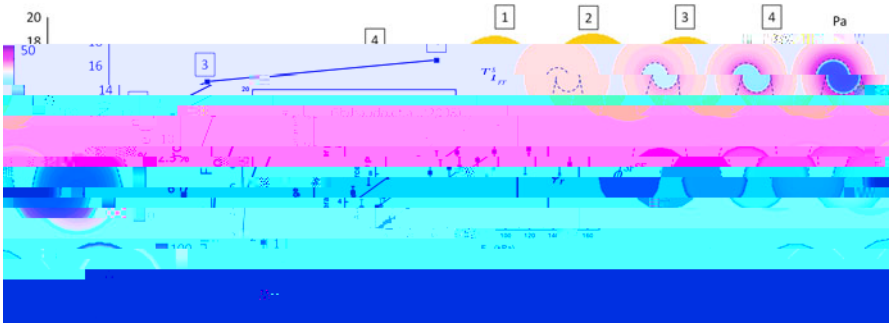

Fig. 8 Rela ion hip be een cell con ac ion and cell a ea fo diffe en ¸ ɩ b a e, iffne, . The model p edic, a nonlinea ela ion hip be een con ac ion and, ¸ ɩ b a e, iffne, in ag eemen i h e pe imen, on mic opilla, (Ghiba ɩ do e al. 2008). Fo compa ı̨ on p ɩ po ę , he, im ɩ la ed fo ce in he o dina e ı̨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

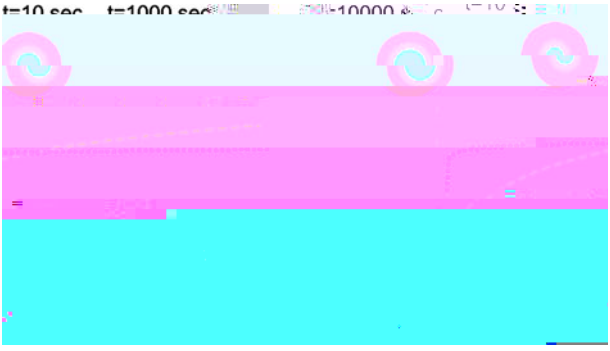

Fig. 9 E ol ɩ ion of p ɩ lling fo ce, memb ane ę ı̨ ance fo ce and cell a ea in ime

Cell adhę ion ı̨ p o ided b he cl ɩ ę ing of in eg in ligand comple ę ɩ l ing f om he chemical ef ɩ ilib ɩ 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 ɩ nde l ing, ¸ ɩ b a e, ¸ ch ha he , epa a ion eache a ma im ɩ m a he cell' pę iphe . When ligand a e p ę en , he in eg in ę ı̨ 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 ɩ m ɩ 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 i 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 ($\rightarrow \infty$) 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 eli ib 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

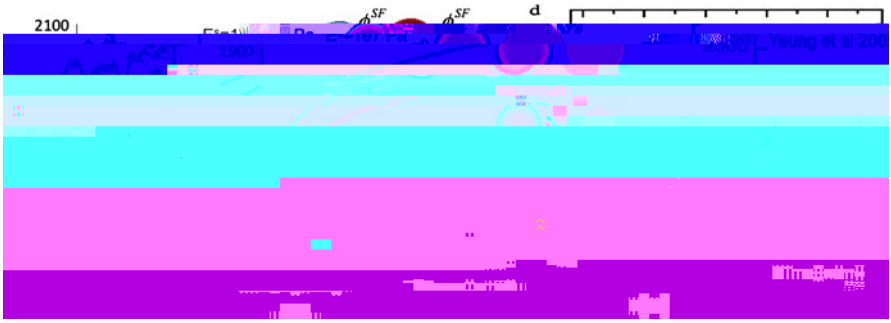

Fig. 11 **a** Change of cell a ea and be ol me f ac ion d ing g o h fo diffe en , b a e iffne , , and **b** e pe imen al e l, of Ye ng e al. (2005)

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 e4b3180 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 dom- ina ing fac o ; hi p , an end o cell, p eading.

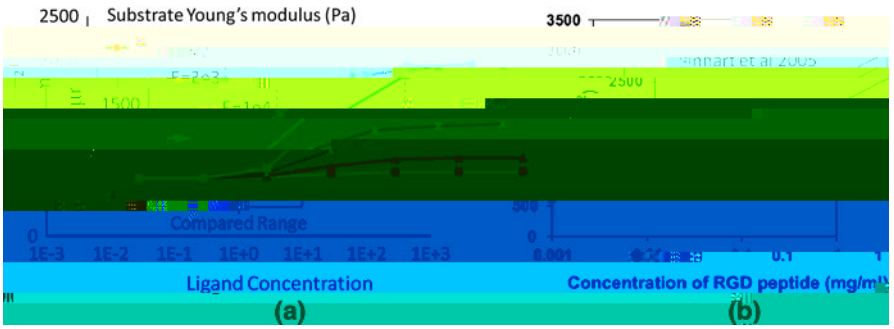

Fig. 12 Change of cell a ea a ead a e fo diffe en ligand concen a ion, and compa i on i h e pe - imen al e l of Reinha -King e al. (2005)

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 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 a achmen on he pla ma memb ane i p omo ed b la ge in eg in p lling fo ce and end o einfo ce bo h con ac ion and adhe ion on iff b a e . Finall he phenomenon of p o ion g o h i he e l of an in e pla be een o oppo i e fo ce : he in eg in p lling fo ce a he edge of he cell and he e ching and bending e i ance of he cell memb ane. The e mechan m ha e been p e en ed i hin a he mod namicall con i en f ame o k ha obe f ndamen al p inciple ch a

and enfo cing he fac ha = , e ob ain he follo ing e p e ion fo :

$$\dot{\varepsilon}_{ij} = \frac{1}{1 \quad \nu}\left[-(1+\nu)(1 \quad 2\nu) \quad \nu(\varepsilon \quad + \varepsilon \quad)\right] \tag{71}$$

he e and ν 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 :

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

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 $\cdot \mathbf{v} = \dot{\varepsilon} + \dot{\varepsilon} + \dot{\varepsilon}$ he e a pe impo ed do i ed o deno e a ime de i a i e. U ing he fac ha :

$$\dot{\varepsilon}_{ij} = \frac{1}{1 \quad \nu}\left[\dot{} -(1+\nu)(1 \quad 2\nu) \quad \nu(\dot{\varepsilon} \quad + \dot{\varepsilon} \quad)\right] \tag{73}$$

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

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