D nie M rous

M the tic Mode of C rti ge Regener tion i Hydroge
Honors Thesis, itten erg ni ersity Dep rt ent of M the tics

Abstract

Bec use of the rge nu er of indi idu s ith c rti ge pro e s, hether due to sports injuries or dise ses such s rthritis, there is edic need for effecti e c rti ge regener tion. To ssist ith the de e op ent of

ce s the chondrocytes co prise on y of the c rti ge ↑o u e HErgge et , 00).

Figure high ights c rti ge tissue, sc ttered ith chondrocytes. Note th t the chondrocytes re not in cont ct ith e ch other, ut re dispersed throughout the ECM. The chondrocytes produce the ECM, hich for s ost of the non ter ↑o u e in c rti ge. HLodish ., 00)

Figure C rti ge Tissue

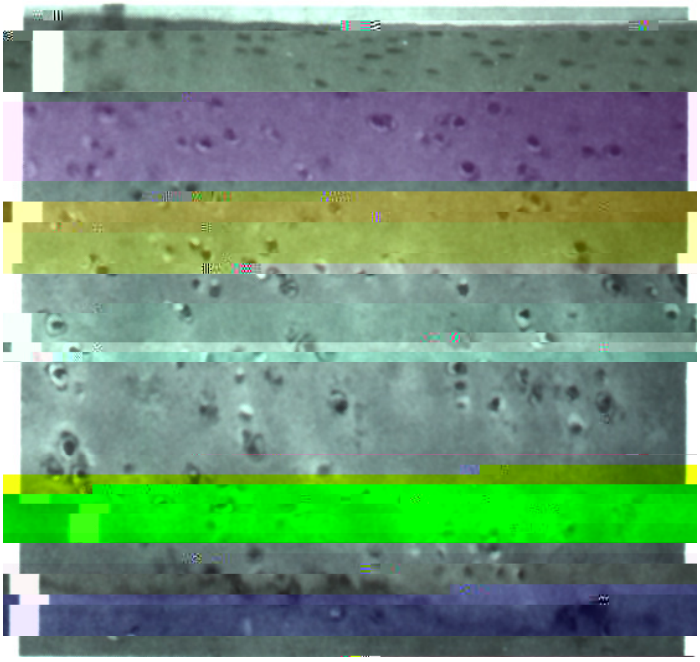

Figure sho s c rti ge tissue. Note ho the chondrocytes Hd r spots) re dispersed throughout the ECM. These ce s re responsi e for ui ding nd int ining the ECM. HNCSU REU)

The ECM itse f is de of t o co ponents, co gen nd proteog yc ns. Appro↕i te y 0 of the dry eight of c rti ge is de of co gen HErgge et , 00). Co gen for s ong, rope i e structures de of ino cid ch ins HLodish ., 00). It is these „ropes‟ th t gi↑e c rti ge its i ity to stretch nd to er te sheer forces. HErgge et , 00) The co gen o ecu es the se↑es re synthesized on ri oso es tt ched to the endop s ic reticu u HER) Hn the chondrocytes) fro indi↑idu ino cids. Further processing occurs in the ER nd Go gi pp r tus, nd co gen str nds Hd ed proco gen t this point) re secreted fro the ce

Hchondrocyte). Once outside the ce , the str nds cross in , for ing the co gen

net or . Hlodish ., 00) Co gen in the ECM is pictured in Figure .

Figure Co gen nd Proteog yc ns in ECM

Figure sho s the co gen nd proteog yc n str nds th t co prise ECM. The co gen is responsi e for the stretching strength of the c rti ge nd is pictured s the thic er fi ri s. The proteog yc ns, hich int in ter

Figure Hy uron n Structure

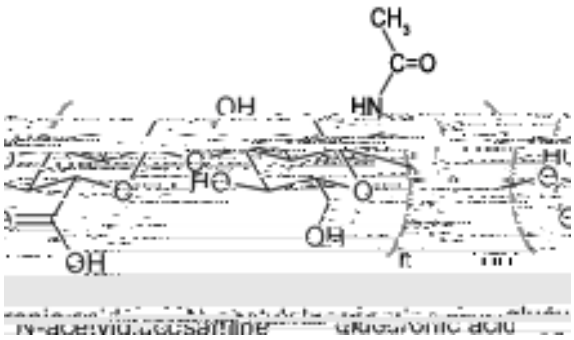

Figure sho s the che ic structure of one unit of hy uron n. Hy uron n for s the sug r c one of the proteog yc n o ecu es. (http .g ycos n.co h t hy uron n.ht)

Hy uron n is de y n enzy e (HA synth se) in the chondrocyte ce e r ne nd is i edi te y tr nsported out of the ce . Ne t, the hy uron n is tt ched (i in er protein) to ggrec n. Aggreg n consists of core protein (synthesized on the ER) tt ched to chondroitin su f te nd er tin su f te sug r ch ins (th t re dded in the Go gi). Aggrec n is then secreted. Thus, the fin proteog yc n structure rese es "centipede" consisting of hy uron n o ecu e ("body") tt ched to u tip e core proteins ("legs"), e ch of hich h e u tip e sug r groups ("feet"). (Lodish ., 00) Figure i ustr tes this structure.

Figure Proteog yc n Structure

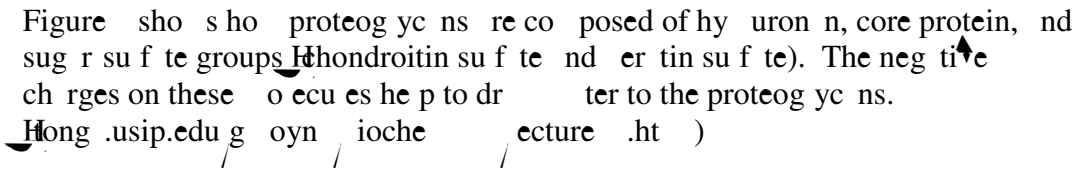

Figure sho s ho proteog yc ns re co posed of hy uron n, core protein, nd sug r su f te groups (chondroitin su f te nd er tin su f te). The neg ti e ch rges on these o ecu es he p to dr ter to the proteog yc ns. (Hong .usip.edu g oyn ioche ecture .ht)

O er , proteog yc n o ecu es h e nu er of neg ti e ch rges on the , ttr cting ter (Lodish ., 00, "Articu r C rti ge", 00). As resu t, eighty percent of the c rti ge itse f is ter. The i ity to dr ter into the c rti ge is i port nt for t e st t o re sons. First, ec use it is fi ed ith ter, c rti ge is e ithst nd co pression forces (Ergge et , 00, "Articu r C rti ge", 00). The inf u x of ter is so it for the diffusion of

produce the ggrec n co p e . Aggrec n then re cts ith hy uron n to for the co p ete proteog yc n unit. Figure high ights these io ogic processes.

Figure Chondrocyte Production of ECM

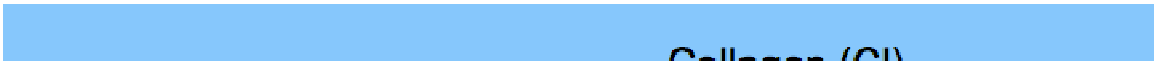

Figure sho s the rious co pounds produced y chondrocyte. First, nutrients diffuse into the ce . The ce es four co pounds ith the nutrients sug r su f tes, the core protein, co gen, nd hy uron n processes , , , nd). The sug r su f tes nd core protein co ine to for ggrec n process). Fin y, hy uron n nd ggrec n co ine to for the co p eted proteog yc n process).

n n

hen c rti ge is d ged H hether due to injury or dise se), there re se er o st c es to rep ir. First, there is not high density of chondrocytes in c rti ge ost of the c rti ge is ECM See Figure). Any d ge th t destroys chondrocytes e ns there re e en fe er of the to int in the c rti ge. This is co pounded y the f ct the chondrocytes oose their i ity to itotic y di ide o fe ne chondrocytes c n e de) nd chondrocytes re dy h e i ited n tur i ity to rep ir defects. Fin y, c rti ge c s ood esse s, so nutrients ust diffuse to the ce s. During the initi for tion of c rti ge, ood is i e to the chondrocytes. In d ged ture

c rti ge, ho e er, ood H ith the corresponding nutrients, etc) is not s i e to ssist ith rep ir. HErgge et , 00) As resu t of c rti ge's i ited n tur i ity for he ing, s injuries H.e. u p on the nee) c n he , hi e rger d ge H.e. sports injury, rthritis) c nnot.

yd o

Bec use of the i ited i ity of c rti ge to rep ir itse f, edic techniques re eing de e oped to f ci it te this he ing process. One such technique in o es surgic y opening the injury site, injecting hydroge to fi the c ity, nd then stitching c rti ge tissue etc c together HErgge et , 00). Specific y, hydroge consists of hy uron n seeded ith chondrocytes Hfro n e xtern source). Hy uron n is the c one of proteog yc ns nd is so e to ind ter, thus e xp ining the ge consistency of the hydroge . The in ide is th t the chondrocytes, deter ining Hthrough sign ing) th t they re not in c rti ge, i egin to produce ECM. The hydroge ser es s ioco p ti e sc ffo d, eeping the chondrocytes sp ced throughout the injury site nd pro iding so e initi structure fro hich c rti ge c n e ui t. The c rti ge is etter e to he ith this sc ffo d in p ce then h ing to fi oid in epte s q H H) 0

The under ying ssu ption is th t the ode represents one ce (chondrocyte), hich h s n ssigned o u e of c rti ge to rep ir. The injury is considered to e he ed hen the ce fi s its ssigned o u e (M) Presu y, of the other ce s in the injury site h e fi ed their o u es s e). This ode h s four ri es corresponding to ture (in ed) ECM (M) in the ssigned o u e, ono eric (un in ed) EMC (Mu), hydroge (H), nd nutrients inside one er ge ce (Nu).

ri es re nor ized to cert in reference ounts. (i.e. the nutrients re nor ized to the ini sur i e e , so the se ine nutrient ount is nything o e is used to rep ir the c rti ge. The in ed tri x, on the other h nd is nor ized to the ide ECM concentr tion nd so represents the t rget he thy e e .) By con ention, the nutrients re st rted t , the e e here no rep ir is occurring. In he thy c rti ge, M nd H Mu $\dot{0}$ In d ged c rti ge, ho e er, M < nd if hydroge is injected into the defect, then H $\dot{0}$ In the ode o e, the initi ic for the regener tion co es fro the nutrient equ tion (Equ tion) if M < , then the Nu concentr tion incre ses (the ce sensing it is not in he thy c rti ge o s ore nutrients into the ce). The nutrient concentr tion is o ered s Mu is produced. Mu concentr tion incre ses hen Nu is o e (s seen fro the first ter in Equ tion). Ne x t, there is che ic re ction et een the un in ed tri x, Mu, nd the hydroge , H, thus for ing in ed tri x, M . This re ction ter ppe rs s the st ter in three of the equ tions (Equ tions , ,). These equ tions ere nu eric y so ed using M the tic (see ppendi x for note oo) for ti e to 0 $0\dot{0}$ The initi conditions ere H $\dot{0}$, Mu

o n Mod

The o e ode , ho e er, is perh ps too si p istic. One of the in issues is th t of ri es do not correspond to specific io ogic co ponents. The ECM is de of co gen nd proteog yc ns nd these re sep r te co pounds. The M nd Mu ri es group these distinct e e ents together. Addition y, hydroge is not re y specific io ogic co pound, though the hy uron n in the hydroge is. Perh ps hy uron n concentr tion ou d e ore io ogic y ccur te ri e. O er , the ode does not re y si u te the ctu io ogy th t is occurring. (Though it is good first ppro i tion since the c rti ge, represented y M , does he if hydroge is injected.)

Mod o d oo

In order to e the ode ore io ogic y re e nt, ne syste of equ tions is needed. The ne ode shou d h e ri es corresponding to io ogic co pounds in o ed ith c rti ge rep ir (s descri ed in the Introduction) inc uding nutrients (Nu) inside the ce (nc uding sug rs, ino cids, etc), co gen (C), proteog yc ns (K), hy uron n (H), core protein (P), su f ted sug r ch ins (S), nd the co p e for ed et een the core protein nd the su f ted sug r ch ins (PS) (cd ed ggrec n). E ch of these co pounds p ys unique ro e in c rti ge rep ir. It is he pfu to sep r te the ode into these ri es so the effects of tering coefficients nd initi conditions for e ch ri e c n e ssessed. Note th t H no represents hy uron n, not hydroge s it did in the st ode . Hy uron n is n ctu io ogic o ecu e nd is coincident y the in co ponent in hydroge . There re other co pounds in o ed ith the regener tion process, ut these re ssu ed to e the in ones. Bio ogic y, there re ssu ed to e three in re ctions in o ing the ri es s descri ed under *B o o c c on* . These re ctions re su rized in ri es s

Nu → Cl, H, S, P

P + S → PS

PS + H → X

Ide y, the ne ode ou d so h ▲e so e ethod for ode ing he thy c rti ge, inf icting d ge t ti e t, nd sho ing ho the c rti ge responds fter the d ge. Fin y, the ode shou d h ▲e "structur " thresho d. The c rti ge needs so e ini ount of structure in order to e e to he H(his structure cou d e fu fi ed y the ounts of proteog yc ns, co gen, hy uron n, or so e co in tion thereof). A o▲e this thresho d H(injury or rger injury ith hydroge injection), the c rti ge shou d he , ut e o the thresho d H(rge injury ithout hydroge injection), the c rti ge shou d not he .

Mod y of on

Using the o▲e specific tions, the fo o ing ode s cre ted

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dNu

ter , the ogic of hich is descri ed o e. Equ tion Hto gen) incre ses ith n incre se in nutrients, ut is inhi ited s co gen is produced H C ter). Equ tion Hhy uron n) incre ses ith n incre se in nutrients, ut is inhi ited y the for tion of proteog yc ns nd hy uron n. A re ction ter et een ggrec n HPS) nd hy uron n HH) re o es hy uron n fro the syste . Equ tion Hcore protein) incre ses ith nutrients, is inhi ited y core protein nd proteog yc n for tion, nd decre ses y re ction ter et een the core protein nd sug r su f tes. Equ tion fo o s si i r ogic to Equ tion , e xcept ith sug r su f tes, inste d of the core protein. Equ tion Hggrec n) incre ses ith re ction ter et een the core protein nd the sug r su f tes, is inhi ited y the for tion of ggrec n, nd decre ses y re ction ter et een ggrec n nd hy uron n. Fin y, equ tion Hproteog yc ns) incre ses ith re ction

represents signific nt injury to the c rti ge. Gr phic so utions of these t o runs

ppe r in Figure .

Figure D ge Inf icted to He thy C rti ge

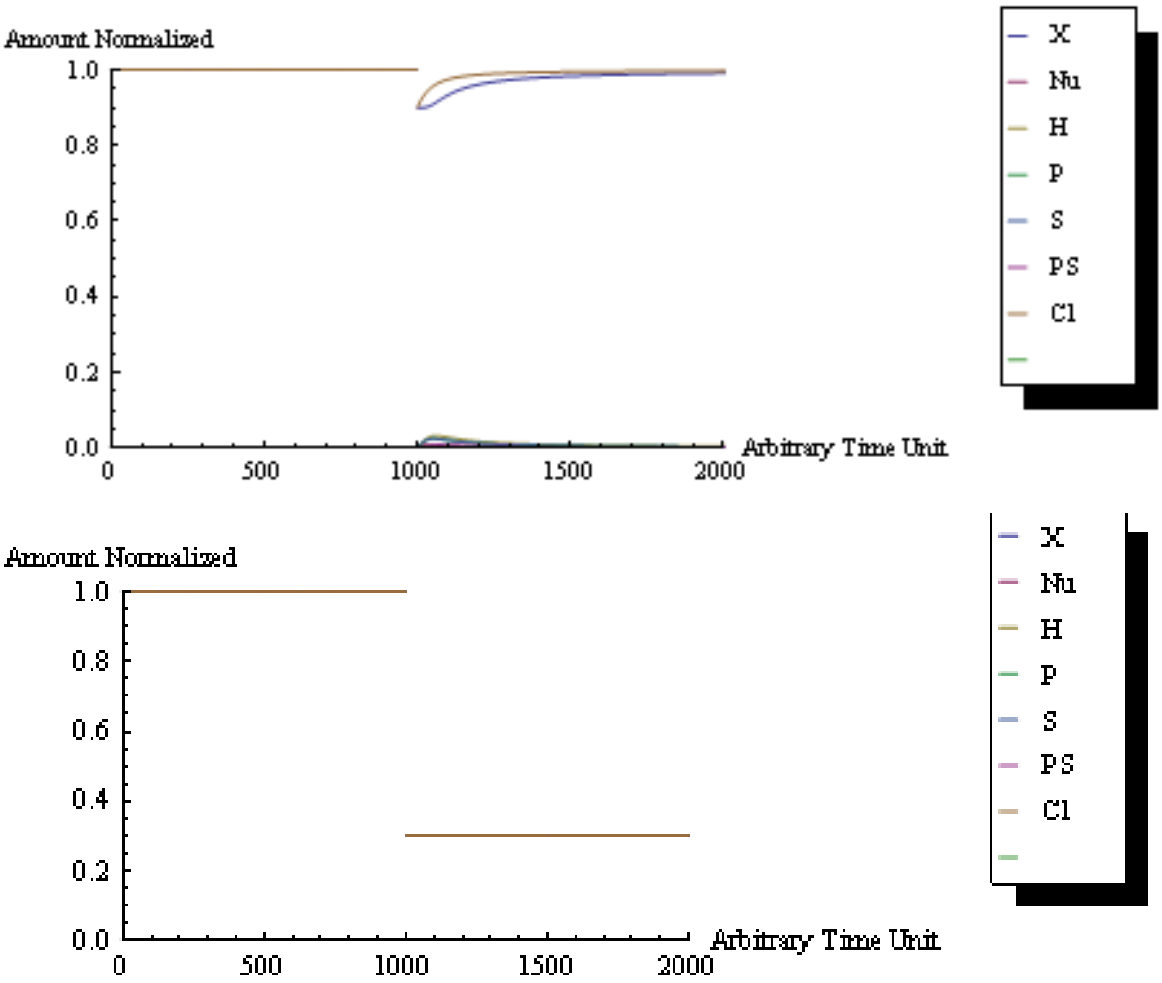
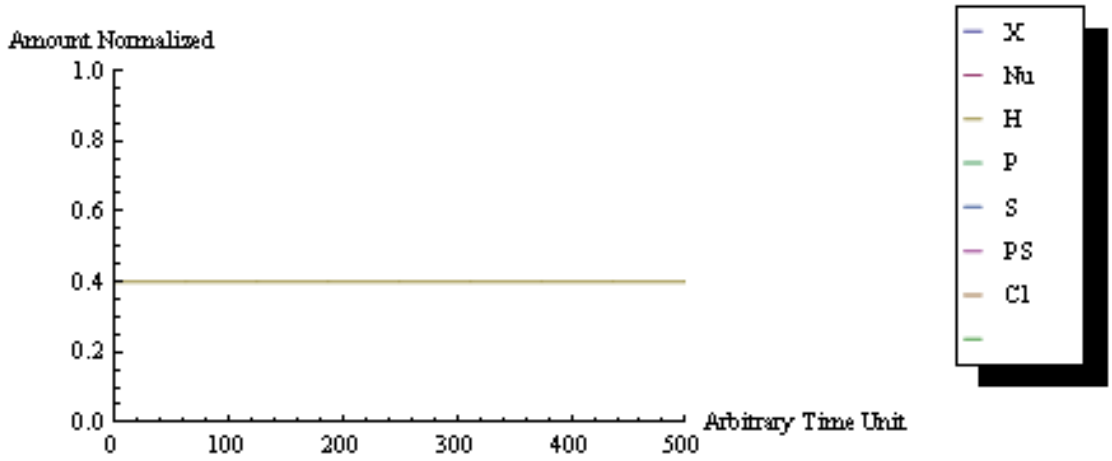


Figure sho s t o so utions of the equ tions here d ge H. nd , respecti e y) s inf icted on the c rti ge. The injury occurs t ti e 0 nd c n 0 e seen y the ju p do n in the co gen nd proteog yc n e e s in oth gr phs. The c rti ge s e to reco er in the first inst nce, s c n e seen y the incre se in proteog yc n nd co gen e e s. The proteog yc ns see to g ehind the co gen. This cou d e the resu t of the p rticu r coefficients th t ere used or the f ct th t ore inter edi tes re required for the production of the proteog yc ns in the ode . Note in the top gr ph th t the nutrients nd other inter edi tes ic on in response to the d ge Heen y the s u ps t the otto of the gr ph). In the second gr ph, the c rti ge s not e to reco er Hs c n e seen y the f t ine t . for the co gen nd proteog yc ns).

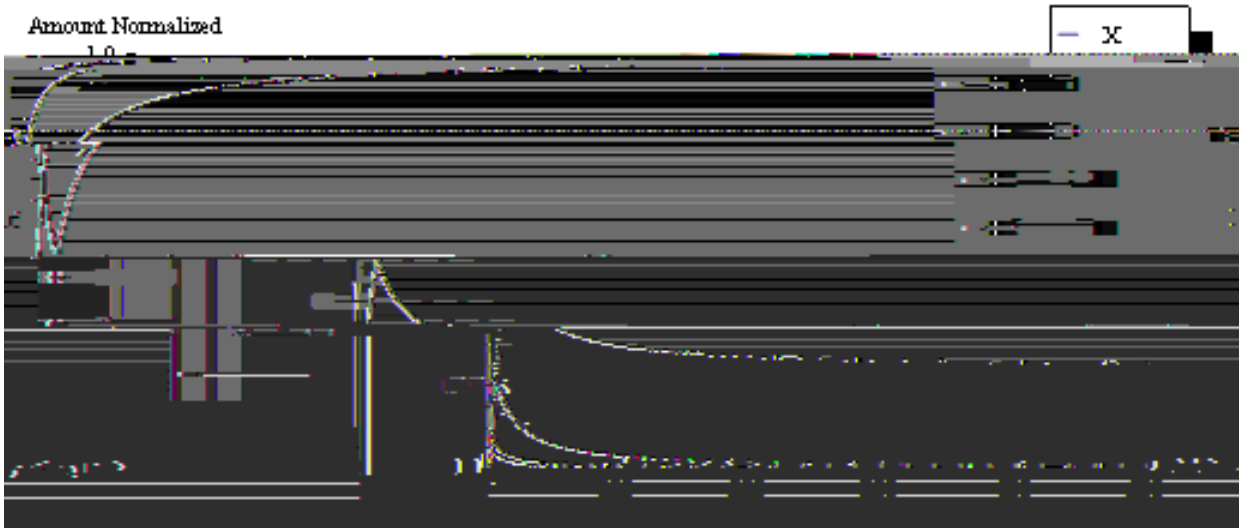
Ne xt, using the s e coefficients nd thresho d for reco ery, series of so utions ere deter ined eginning ith d ged c rti ge HX nd C e o) ith rious ounts of injected hy uron n Hn the for of hydroge). Figure sho s h t h ppens hen fu d ged c rti ge HC X) is injected ith nd hy uron n Hno reco ery nd fu reco ery, respecti e y). The third p ot is c ose up of ti e of the second p ot note the ho the rious inter edi tes re turned on to rep ir the d ge.

Figure Fu y D ged C rti ge ith Hydroge Injections

H Hy uron n)



H Hy uron n)



H Hy uron n, ti e)

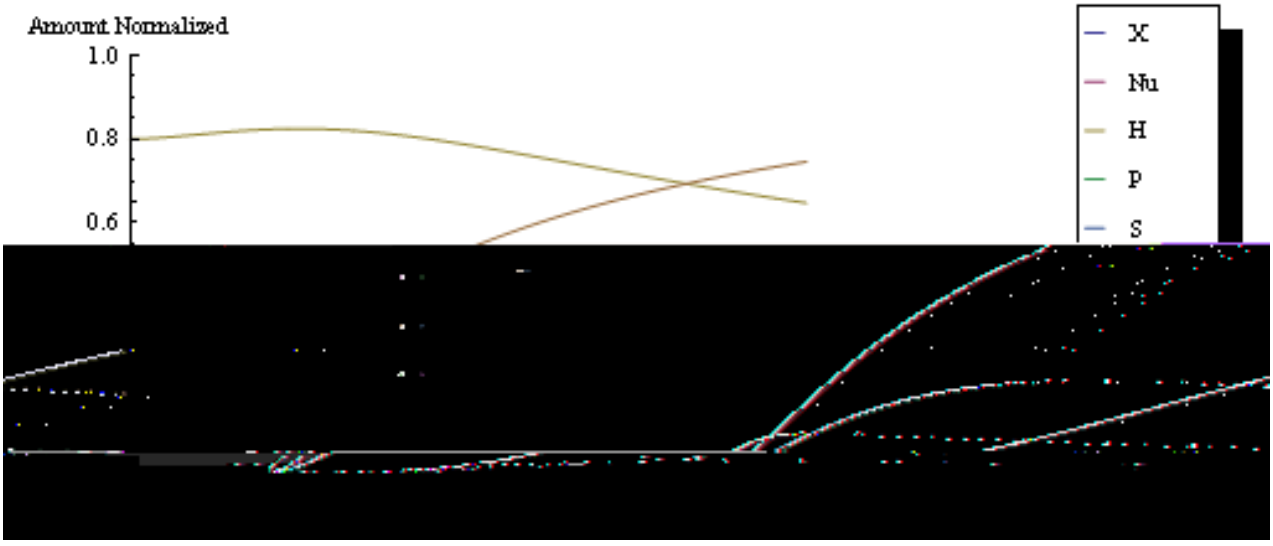
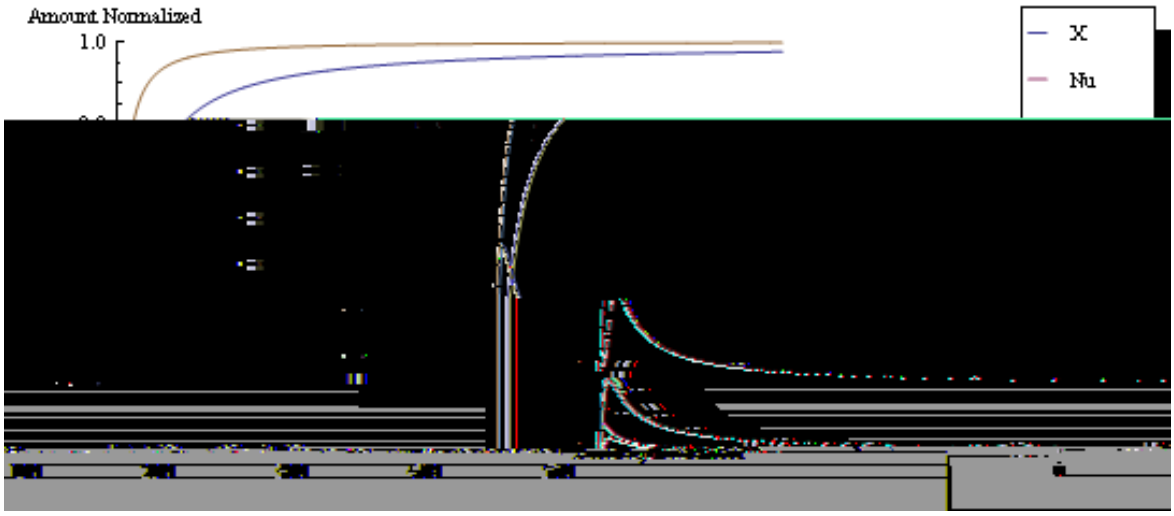


Figure sho s ho d ged c rti ge responds ith hydroge injections. In the first p ot, . hy uron n is injected, hich is not enough to he the c rti ge in this inst nce. Thus, the hy uron n HH) e e st ys t . nd the co gen HC) nd proteog yc n HX) e e s st y t . In the second p ot, . hy uron n is injected. This is enough to he the c rti ge s c n e seen y the incre se of the co gen nd proteog yc ns to rds . rious inter edi tes re so produced nd used s c n e seen in the second nd third p ots s the su st nces th t pe nd then co e c do n to zero.

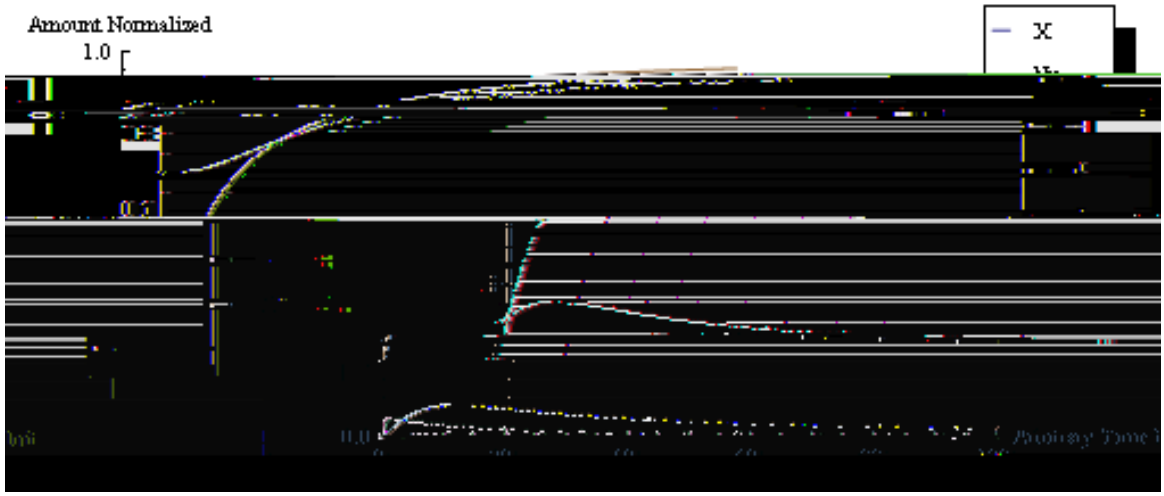
Ne t, the proteog yc n nd co gen e e s in the d ge c rti ge ere st rted o e Hnot co p ete y d ged). Different ounts of hydroge Hhy uron n) ere injected nd depending on the tot structure th t s present, the c rti ge either s regener ted or st yed d ged. Figure sho s so e gr phic so utions to these runs. In the first p ot Hn Figure), the c rti ge is e to reco er despite the hy uron n e e on y eing t H here it s not e to reco er in Figure) ec use there is so e co gen nd proteog yc ns present. The second p ot h s o e e s of co gen nd hy uron n H nd , respecti e y), ut is e to reco er ec use of the high e e of proteog yc ns H). No regener tion is seen in the third p ot ec use the structure of the syste is not o e the thresho d e e .

Figure 0 P rti y D ged C rti ge ith Hydroge Injections

HH ˙0 , C X ˙0)



HH ˙0 , C ˙0 , X ˙0)



HH 0̇ , C 0̇ , X 0̇)

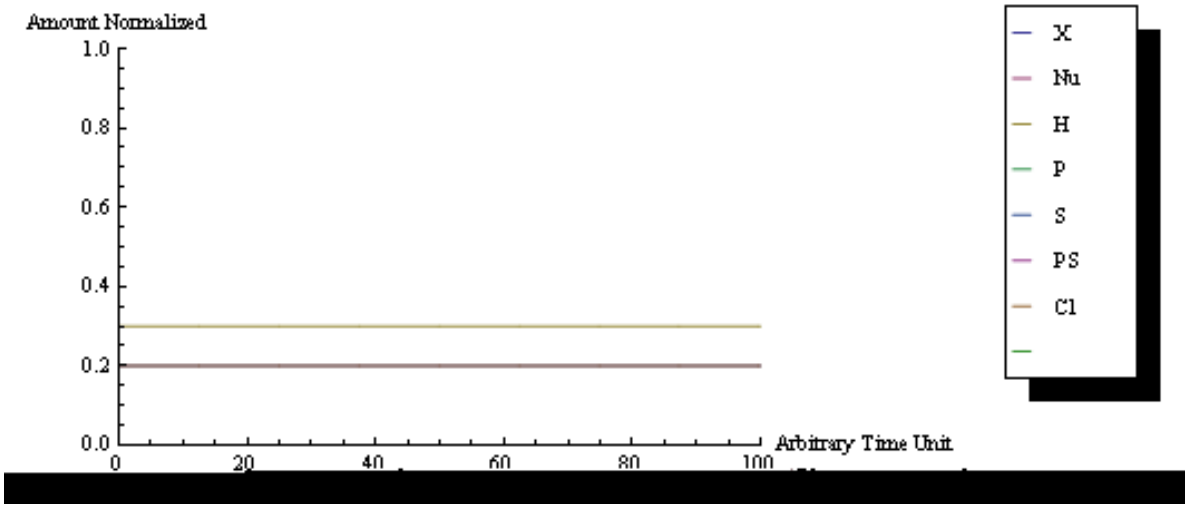


Figure sho s ho p rti y d ged c rti ge responds to rious hydroge injections. In the first p ot, the co gen nd proteog yc ns re initi y t , indic ting p rti y d ged c rti ge. Hy uron n is injected H) nd the c rti ge he s, s c n e seen y the incre se in proteog yc ns nd co gen to rds . In the second p ot, the c rti ge is sti p rti y d ged H , X) nd hy uron n is injected. Despite the f ct th t there is ess hy uron n present th n in the pre ious inst nce, the c rti ge sti he s ec use there re ore proteog yc ns H s.) present initi y. In the third p ot the c rti ge is p rti y d ged H , X), ut not enough hy uron n H) is injected to pro ote he ing, s c n e seen y the f t ine H orresponding to co gen nd proteog yc ns) t .

Conclusion

Despite the i pro e ents in the ne ode , there is sti or to e done in ode ing c rti ge regener tion. First, there re so e io ogic questions th t re in to

References

Appendix