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adaptation and disease Mechanics in skeletal development,

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doi: 10.1098/rsta.2000.0546 Phil. Trans. R. Soc. Lond. A 2000 **358**, 565-578

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Mechanics in skeletal development,
adaptation and disease nics in skeletal developme
adaptation and disease adaptation and disease
BY MARJOLEIN C. H. VAN DER MEULEN¹

AND PATRICK J. PRENDERGAST²

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Phool of Mechanical and Aerospace Engineering, Cornell Unidensity Upson Hall, Ithaca, NY 14853, USA (mcv3@cornell.edu) *hool of Mechanical and Aerospace Engineering, Cornell Un Upson Hall, Ithaca, NY 14853, USA* (mcv3@cornell.edu)
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 μ and μ , related (ppicmetreated).
Mechanical loading plays an important role in the development, adaptation and func-
tion of the vertebrate skeleton, but our understanding of this role is incomplete. The Mechanical loading plays an important role in the development, adaptation and func-
tion of the vertebrate skeleton, but our understanding of this role is incomplete. The
influence of mechanics initiates during early embry tion of the vertebrate skeleton, but our understanding of this role is incomplete. The influence of mechanics initiates during early embryogenesis and continues throughout tion of the vertebrate skeleton, but our understanding of this role is incomplete. The influence of mechanics initiates during early embryogenesis and continues throughout life, determining the geometric and material chara influence of mechanics initiates during early embryogenesis and continues throughout
life, determining the geometric and material characteristics of the skeleton. In this
paper, the current understanding of bone mechano-bi life, determining the geometric and material characteristics of the skeleton. In this paper, the current understanding of bone mechano-biology will be reviewed, high-
lighting important open questions. Advancing our knowle paper, the current understanding of bone mechano-biology will be reviewed, high-
lighting important open questions. Advancing our knowledge in this field, coupled
with important recent biological advances, has exciting pot lighting important open questions. Adviewith important recent biological advancement
methods and treatments in the future.

ments in the future.
Keywords: bone; mechanics; computer simulation;
adantation: cell mechanics: imaging m the ruture.
ds: bone; mechanics; computer simulat
adaptation; cell mechanics; imaging

1. Introduction and historical background

ICAL
Gineering
(Ces The mineralized skeleton of vertebrates serves several important functions, including
structural support for the organism; storage of ions, particularly calcium; produc-
tion of red blood cells: and protection of vital org The mineralized skeleton of vertebrates serves several important functions, including
structural support for the organism; storage of ions, particularly calcium; produc-
tion of red blood cells; and protection of vital org The mineralized skeleton of vertebrates serves several important functions, including structural support for the organism; storage of ions, particularly calcium; production of red blood cells; and protection of vital organs such as the heart and lungs.
The structural role of the skeleton is particularly int tion of red blood cells; and protection of vital organs such as the heart and lungs.
The structural role of the skeleton is particularly interesting to physicists and engi-
neers because bone is an adaptive, living tissue

The structural role of the skeleton is particularly interesting to physicists and engi-
neers because bone is an adaptive, living tissue containing cells that respond to their
physical environment. Form follows function. H neers because bone is an adaptive, living tissue containing cells that respond to their
physical environment. Form follows function. Historically, most of our knowledge
comes from treating bone as a conventional engineerin physical environment. Form follows function. Historically, most of our knowledge comes from treating bone as a conventional engineering material, studying bone tiscomes from treating bone as a conventional engineering material, studying bone tissue and whole bones when placed under loads in the laboratory. This approach does not consider that bone is a living tissue nor account for sue and whole bones when placed under loads in the laboratory. This approach does
not consider that bone is a living tissue nor account for the influence of mechanical
loading in regulating the biological processes that oc The mechanical ture. Separating the mechanical processes that occur to form the skeletal structure. Separating the mechanics from the biology is impossible: mechano-biological I loading in regulating the biological processes that occur to form the skeletal structure. Separating the mechanics from the biology is impossible: mechano-biological coupling initiates during early development when the ture. Separating the mechanics from the biology is impossible: mechano-biological
coupling initiates during early development when the primordial cellular structure
first experiences deformations and pressures, and continu coupling initiates during early development when the primordial cellular structure
first experiences deformations and pressures, and continues throughout the growth,
development and ageing of the organism. Understanding th first experiences deformations and pressures, and continues throughout the growth, development and ageing of the organism. Understanding the influence of biophysical stimuli on skeletal growth and adaptation is of great re development and ageing of the organism. Underst
stimuli on skeletal growth and adaptation is of gr
diseases such as osteoporosis and osteoarthritis.
The structural adaptation of the skeleton has diseases such as osteoporosis and osteoarthritis.
The structural adaptation of the skeleton has been one of the most fascinating

problems in the history of science. Galileo (1638) observed that longer bones had to The structural adaptation of the skeleton has been one of the most fascinating
problems in the history of science. Galileo (1638) observed that longer bones had to
be thicker for the same structural strength, and diagramm problems in the history of science. Galileo (1638) observed that longer bones had to
be thicker for the same structural strength, and diagrammed the required scaling in
his *Discorsi e Dimostrazioni Matematiche intorno a d* his *Discorsi e Dimostrazioni Matematiche intorno a due nuove scienze*. In discussing
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Figure 1. (*a*) Culmann's diagram of the stress trajectories in a crane, (*b*) Wolff's drawing of the trabecular orientation in the upper part of the femur, and (*c*) a photograph of the cross-section of the upper part of Figure 1. (a) Culmann's diagram
trabecular orientation in the upp
of the upper part of the femur. $\overline{5}$ of the upper part of the femur.
heritable and acquired traits in *On the origin of species*, Darwin (1859) noted that

heritable and acquired traits in *On the origin of species*, Darwin (1859) noted that
flying wild ducks have proportionally larger wing bones and smaller leg bones than
their non-flying domestic relatives. Many natural ph flying wild ducks have proportionally larger wing bones and smaller leg bones than flying wild ducks have proportionally larger wing bones and smaller leg bones than
their non-flying domestic relatives. Many natural philosophers of the 19th century
used mechanical principles to explain bone geometry, inc their non-flying domestic relatives. Many natural philosophers of the 19th century
used mechanical principles to explain bone geometry, including, most famously, Wolff
(1892) in his *Das Gesetz der Transformation der Knoch* used mechanical principles to explain bone geometry, including, most famously, Wolff (1892) in his *Das Gesetz der Transformation der Knochen*. Wolff examined many pathologically healed bones to argue that bone tissue was pathologically healed bones to argue that bone tissue was distributed within the pathologically healed bones to argue that bone tissue was distributed within the organ to best resist mechanical forces. A famous exchange between the Swiss engi-
neer Culmann and his colleague von Meyer has become the def **MATHEMATICAL,
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& ENGINEERING
SCIENCES** organ to best resist mechanical forces. A famous exchange between the Swiss engi-
neer Culmann and his colleague von Meyer has become the defining 'eureka' episode
of modern biomechanics. The internal architecture of a fem of modern biomechanics. The internal architecture of a femur was being demonstrated by von Meyer, and Culmann, who developed the methods of graphic statics, exclaimed 'That's my crane' (figure 1). These concepts were furth of modern biomechanics. The internal architecture of a femur was being demonstrated by von Meyer, and Culmann, who developed the methods of graphic statics, exclaimed 'That's my crane' (figure 1). These concepts were furt generalized by von Meyer, and Culmann, who developed the methods of graphic statics, exclaimed 'That's my crane' (figure 1). These concepts were further developed and generalized by D'Arcy Thompson (1917) in his influentia generalized by D'Arcy Thompson (1917) in his influential work On growth and form.
The mechanism of bone adaptation was first addressed by the German embryologist
Wilhelm Roux (1895), who proposed the controversial hypothe The mechanism of bone adaptation was first addressed by the German embryologist Wilhelm Roux (1895), who proposed the controversial hypothesis that bone cells compete for a functional stimulus, \hat{u} *la* Darwin, and en compete for a functional stimulus, \dot{a} la Darwin, and engage in a struggle for survival that leads to *Selbstgestaltung* (self-organization).

Roux and his turn-of-the-century contemporaries were not able to advance much that leads to *Selbstgestaltung* (self-organization).
Roux and his turn-of-the-century contemporaries were not able to advance much
beyond this philosophical and descriptive understanding of the role of mechanics in
skelet Roux and his turn-of-the-century contemporaries were not able to advance much
beyond this philosophical and descriptive understanding of the role of mechanics in
skeletal growth. As the century progressed, biology increasi beyond this philosophical and descriptive understanding of the role of mechanics in
skeletal growth. As the century progressed, biology increasingly reduced the organ-
ism to the molecular level, and the interest in mechan skeletal growth. As the century progressed, biology increasingly reduced the organism to the molecular level, and the interest in mechanics and other biophysical factors waned. However, in recent years, the emergence of se ism to the molecular level, and the interest in mechanics and other biophysical factors
waned. However, in recent years, the emergence of several new technologies has fos-
tered a re-examination of the old questions relati waned. However, in recent years, the emergence of several new technologies has fos-
tered a re-examination of the old questions relating to the mechanical regulation of
tissue growth and adaptation. The first of these is c tissue growth and adaptation. The first of these is computer-based structural modelling, which allows a more valid analysis of effects of physical forces within complex tissue growth and adaptation. The first of these is computer-based structural modelling, which allows a more valid analysis of effects of physical forces within complex skeletal geometries; the second is molecular biology, elling, which allows a more valid analysis of effects of physical forces within complex
skeletal geometries; the second is molecular biology, which localizes individual gene
expression and protein synthesis under different skeletal geometries; the second is molecular biology, which localizes individual gene
expression and protein synthesis under different mechanical forces; and the third is
the tremendous advances in imaging technologies, wh *Phil. Trans. R. Soc. Lond.* A (2000)

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Mechanics in sk[eletal development, adapt](http://rsta.royalsocietypublishing.org/)ation and disease ⁵⁶⁷ Downloaded from rsta.royalsocietypublishing.org

ribution of cortical and cancellous tissue in a long cells (osteoblast, osteocyte, and the osteoclast).

*AATHEMATICAL,
'HYSICAL
k ENGINEERING
CIENCES* microstructural characteristics of tissues and the role of cells in constructing and microstructural characteristics of tissues and the role of cells in constructing and
maintaining skeletal strength. In this paper, our current understanding of the role of
mechanical forces in skeletal biology will be used microstructural characteristics of tissues and the role of cells in constructing and
maintaining skeletal strength. In this paper, our current understanding of the role of
mechanical forces in skeletal biology will be used mechanical forces in skeletal biology will be used to highlight the interaction between
the physical and biological sciences, and motivate important future questions.

2. Form and function in bone

2. Form and function in bone
The musculo-skeletal system consists of bones, blood vessels, nerves, ligaments, ten-
dons muscles and cartilage which work together to perform the structural and kine-The musculo-skeletal system consists of bones, blood vessels, nerves, ligaments, ten-
dons, muscles and cartilage, which work together to perform the structural and kine-
matic functions of the organism. These musculoskele The musculo-skeletal system consists of bones, blood vessels, nerves, ligaments, ten-
dons, muscles and cartilage, which work together to perform the structural and kine-
matic functions of the organism. These musculoskele Chases and cartilage, which work together to perform the structural and kine-

U matic functions of the organism. These musculoskeletal tissues all have a composite

O structure of cells embedded in a matrix produced by t matic functions of the organism. These musculoskeletal tissues all have a competructure of cells embedded in a matrix produced by the cells themselves. Whil focus on the skeleton here, analogous organization exists within (*a*) *Bone structure*

 (a) *Bone structure*
The geometry and structure of a bone consists of a mineralized tissue populated
th cells. This bone tissue has two distinct structural forms: dense cortical bone The geometry and structure of a bone consists of a mineralized tissue populated
with cells. This bone tissue has two distinct structural forms: dense cortical bone
(apparent density greater than $1.5 \times cc^{-1}$)) and lattice-The geometry and structure of a bone consists of a mineralized tissue populated with cells. This bone tissue has two distinct structural forms: dense cortical bone (apparent density greater than 1.5 g cc^{-1})) and latti

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local mechanical and biochemical stimuli. Adapted from Caplan (1994).

local mechanical and biochemical stimuli. Adapted from Caplan (1994).
density less than 1.0 g cc^{-1}), see figure 2*a*. Reilly & Burstein (1975) demonstrated
that cortical bone is a nearly transversely isotropic materia density less than 1.0 g cc^{-1}), see figure $2a$. Reilly & Burstein (1975) demonstrated
that cortical bone is a nearly transversely isotropic material. The structure is made up
of osteons, longitudinal cylinders of bone density less than 1.0 g cc⁻¹), see figure 2*a*. Reilly & Burstein (1975) demonstrated
that cortical bone is a nearly transversely isotropic material. The structure is made up
of osteons, longitudinal cylinders of bone c that cortical bone is a nearly transversely isotropic material. The structure is made up of osteons, longitudinal cylinders of bone centred around blood vessels. Cancellous
bone, on the other hand, is an orthotropic material, with a porous architecture
formed by individual struts or trabeculae (Gibson 1985). bone, on the other hand, is an orthotropic material, with a porous architecture formed by individual struts or trabeculae (Gibson 1985). This high surface area structure represents only 20% of skeletal mass, but has 50% of the metabolic activity. The density of cancellous bone varies significantly, a structure represents only 20% of skeletal mass, but has 50% of the metabolic activity.
The density of cancellous bone varies significantly, and its mechanical behaviour is
influenced by density and architecture. Carter & The density of cancellous bone varies significantly, and its mechanical behaviour is influenced by density and architecture. Carter $\&$ Hayes (1977) first identified that the modulus and strength of both tissue structure modulus and strength of both tissue structures are functions of the apparent density.
(*b*) *Cells and matrix*

The material of cortical and cancellous bone consists of cells in a mineralized matrix. All skeletal cells are known to differentiate from a common precursor cell pool: the mesenchymal stem cells of the embryo (figure 3). Mechanical stimuli conmatrix. All skeletal cells are known to differentiate from a common precursor cell
pool: the mesenchymal stem cells of the embryo (figure 3). Mechanical stimuli con-
siderably influence the stem cell differentiation pathwa pool: the mesenchymal stem cells of the embryo (figure 3). Mechanical stimuli considerably influence the stem cell differentiation pathway and the resulting tissue type. Manipulation and control of stem cell differentiatio siderably influence the stem cell differentiation pathway and the resulting tissue
type. Manipulation and control of stem cell differentiation holds considerable tissue
engineering promise and has recently been receiving m \Box type. Manipulation and control of stem cell differentiation holds considerable tissue
 \Box \bigcirc engineering promise and has recently been receiving much commercial and ethi-
 \Box \bigcirc cal attention. In addition to cal attention. In addition to precursor cells, three principal cell types are present cal attention. In addition to precursor cells, three principal cell types are present
in bone: osteoblasts, osteocytes and osteoclasts (figure $2b$). Osteoblasts are active
bone-forming cells. All bone surfaces are covere in bone: osteoblasts, osteocytes and osteoclasts (figure $2b$). Osteoblasts are active
bone-forming cells. All bone surfaces are covered by a single layer of precursor cells
and resting osteoblasts. Upon activitation, ost bone-forming cells. All bone surfaces are covered by a single layer of precursor cells
and resting osteoblasts. Upon activitation, osteoblasts secrete osteoid, the organic
extracellular matrix into which mineral crystals a and resting osteoblasts. Upon activitation, osteoblasts secrete osteoid, the organic extracellular matrix into which mineral crystals are deposited. The organic matrix contains 90% collagen and a ground substance consistin extracellular matrix into which mineral crystals are deposited. The organic matrix contains 90% collagen and a ground substance consisting of large protein polysaccharides and a variety of matrix proteins. Gaps in the coll contains 90% collagen and a ground substance consisting of large protein polysaccharides and a variety of matrix proteins. Gaps in the collagen fibrils serve as mineral nucleation sites for calcium phosphate, which forms t

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is a composite of a ductile polymeric (collagen) phase and a strong ceramic phase.
This combination gives bone its unique mechanical qualities of high strength and
toughness (Currey 1984). **HYSICAL**
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CIENCES is a composite of a ductile polymeric (collagen) phase and a strong ceramic phase. is a composite of a ductile
This combination gives bo
toughness (Currey 1984).
Approximately 15% of o is combination gives bone its unique mechanical qualities of high strength and
ughness (Currey 1984).
Approximately 15% of osteoblasts become entrapped in their own matrix to be-
me osteocytes. Osteocytes have a vast three

toughness (Currey 1984).
Approximately 15% of osteoblasts become entrapped in their own matrix to be-
come osteocytes. Osteocytes have a vast three-dimensional network of cell processes
(canaliculi), providing nourishment Approximately 15% of osteoblasts become entrapped in their own matrix to become osteocytes. Osteocytes have a vast three-dimensional network of cell processes (canaliculi), providing nourishment and cell-cell interactions. come osteocytes. Osteocytes have a vast three-dimensional network of cell processes (canaliculi), providing nourishment and cell-cell interactions. Due to their location throughout bone tissue and the extensive canalicular (canaliculi), providing nourishment and cell-cell interactions. Due to their location throughout bone tissue and the extensive canalicular network, osteocytes are assumed to be a vital component of sensing mechanical signa tion throughout bone tissue and the extensive canalicular network, osteocytes are assumed to be a vital component of sensing mechanical signals. Nutrients are essential for the vitality of bone tissue and are obtained from \Box most osteocytes to lie within 150 μ m of a blood vessel, resulting in a high cellular tial for the vitality of bone tissue and are obtained from the blood supply, limiting
most osteocytes to lie within 150 μ m of a blood vessel, resulting in a high cellular
density: 25 000 osteocytes within 1 mm^2 of most osteocytes to lie within $150 \mu m$ of a blood vessel, resulting in a high cellular density: $25\,000$ osteocytes within 1 mm^2 of bone tissue (Baron 1996). The third cell type, the osteoclast, has a different orig type, the osteoclast, has a different origin than the other two, and is presumed to arise from the fusion of blood cells. Osteoclasts are large distinctive multinucleated cells that resorb bone. By sealing to a bone surface, the osteoclast forms an acidic cavity, which effectively dissolves the underlyin cells that resorb bone. By sealing to a bone surface, the osteoclast forms an acidic

(*c*) *Bone growth and maintenance*

Bone forms by two different developmental processes: endochondral ossification
and intramembranous ossification. Endochondral ossification involves an intermedi-
ate tissue stage, cartilage, not present in intramembranous Bone forms by two different developmental processes: endochondral ossification and intramembranous ossification. Endochondral ossification involves an intermedi-
ate tissue stage, cartilage, not present in intramembranous formation. The long bones
all form endochondrally. In these bones, development and intramembranous ossification. Endochondral ossification involves an intermediate tissue stage, cartilage, not present in intramembranous formation. The long bones
all form endochondrally. In these bones, development begins with the condensation
of mesenchymal cells, which differentiate into chondro all form endochondrally. In these bones, development begins with the condensation
of mesenchymal cells, which differentiate into chondrocytes (figure 3), creating a car-
tilage prepattern of the skeleton. The first bony ti of mesenchymal cells, which differentiate into chondrocytes (figure 3), creating a car-
tilage prepattern of the skeleton. The first bony tissue, known as the bone collar,
appears spontaneously surrounding the midshaft. Th tilage prepattern of the skeleton. The first bony tissue, known as the bone collar,
appears spontaneously surrounding the midshaft. Thereafter, ossification proceeds
axially towards each bone end. An identical temporal seq appears spontaneously surrounding the midshaft. Thereafter, ossification proceeds
axially towards each bone end. An identical temporal sequence of ossification occurs
at each location: the cartilage calcifies, blood vessel axially towards each bone end. An identical temporal sequence of ossification occurs
at each location: the cartilage calcifies, blood vessels invade the site, and the car-
tilage is resorbed and replaced by bone. This sequ at each location: the cartilage calcifies, blood vessels invade the site, and the car-
tilage is resorbed and replaced by bone. This sequence is regulated by a cascade
of factors including genetic regulatory factors, syste ICAL
GINEERING
VCES tilage is resorbed and replaced by bone. This sequence is regulated by a cascade
of factors including genetic regulatory factors, systemic hormones, growth factors
and mechano-biologic effects (Vortkamp *et al.* 1996). The of factors including genetic regulatory factors, systemic hormones, growth factors
and mechano-biologic effects (Vortkamp *et al.* 1996). The timing of these signals is
critical to the outcome. In the developing embryo, t embryo, the first ossification of cartilage
is coincident with the first muscle contractions; if a muscle is immobilized in the
embryo, a distorted and disorganized bone forms (Wong *et al.* 1993), demonstrating
the link b $\frac{1}{2}$ $\frac{1}{2}$ critical to the outcome. In the developing embryo, the first ossification of cartilage $\frac{1}{2}$ is coincident with the first muscle contractions; if a muscle is immobilized in the hbryo, a distorted and disorganized bone forms (Wong *et al.* 1993), demonstrating e link between mechanics and bone tissue formation.
After embryonic bone formation, the skeleton continues to grow in length by divid-
 σ the link between mechanics and bone tissue formation.
After embryonic bone formation, the skeleton continues to grow in length by divid-

ing and enlarging cartilage cells, which then ossify to form cancellous bone. Growth \geq in bone diameter occurs by direct deposition of bone on existing bone surfaces, ing and enlarging cartilage cells, which then ossify to form cancellous bone. Growth
in bone diameter occurs by direct deposition of bone on existing bone surfaces,
accompanied by resorption of outer surfaces. As the skele in bone diameter occurs by direct deposition of bone on existing bone surfaces, accompanied by resorption of outer surfaces. As the skeleton continues to develop, mechanical forces generate an ever increasing influence on accompanied by resorption of outer surfaces. As the skeleton continues to develop,
mechanical forces generate an ever increasing influence on the forming bone archi-
tectures and geometries. Cellular proliferation increase mechanical forces generate an ever increasing influence on the forming bone architectures and geometries. Cellular proliferation increases skeletal size and needs to be exquisitely controlled to maintain form and proportio \bigcup tectures and geometries. Cellular proliferation increases skeletal size and needs to be

 $\overline{\mathbf{S}}$ tural integrity and also creates more orderly tissue structures. Remodelling involves
coupled resorption and formation on all bone surfaces in a well-defined sequence of
events. Frost (1973) described the remodelling seque tural integrity and also creates more orderly tissue structures. Remodelling involves coupled resorption and formation on all bone surfaces in a well-defined sequence of coupled resorption and formation on all bone surfaces in a well-defined sequence of
events. Frost (1973) described the remodelling sequence as activation of the surface,
resorption by osteoclasts, reversal, formation by os events. Frost (1973) described the remodelling sequence as activation of the surface, resorption by osteoclasts, reversal, formation by osteoblasts, and return to quiescence of the surface. In the adult, remodelling serves resorption by osteoclasts, reversal, formation by osteoblasts, and return to quiescence
of the surface. In the adult, remodelling serves to repair, renew and adapt bone tissue.
A primary function of remodelling is to repla

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resulting from repetitive functional loading (Martin & Burr 1989). Without this conresulting from repetitive functional loading (Martin & Burr 1989). Without this continuous repair process, preventing the accumulation of damage would require a much larger skeleton. resulting from rep
tinuous repair pro
larger skeleton.
Another impor ntiative important mechanically mediated process is bone fracture repair. A frac-
Another important mechanically mediated process is bone fracture repair. A frac-
re-initiates a multistage sequence of tissue regeneration,

larger skeleton.
Another important mechanically mediated process is bone fracture repair. A fracture initiates a multistage sequence of tissue regeneration, which recapitulates tissue differentiation and development. There is also evidence of this process in individual, ture initiates a multistage sequence of tissue regeneration, which recapitulates tissue
differentiation and development. There is also evidence of this process in individual,
fractured trabeculae (Fazzalari 1993). Initiall differentiation and development. There is also evidence of this process in individual,
fractured trabeculae (Fazzalari 1993). Initially a large granuloma forms containing
undifferentiated mesenchymal stem cells whose diffe fractured trabeculae (Fazzalari 1993). Initially a large granuloma forms containing
undifferentiated mesenchymal stem cells whose differentiation is once again regulated
by genetic and epigenetic factors. Following this im undifferentiated mesenchymal stem cells whose differentiation is once again regulated
by genetic and epigenetic factors. Following this immediate trauma response, the cells
differentiate into cartilage to stabilize the fra by genetic and epigenetic factors. Following this immediate trauma response, the cells
differentiate into cartilage to stabilize the fracture. The initial bridging and immo-
bilization are performed by tissues that can tol differentiate into cartilage to stabilize the fracture. The initial bridging and immo-
bilization are performed by tissues that can tolerate the high strains that preclude
bone formation (Perren 1979). Thereafter, endochon bilization are performed by tissues that can tolerate the high strains that preclude
bone formation (Perren 1979). Thereafter, endochondral ossification of the cartilage
occurs and bone forms. Finally, the new bone is remo bone formation (Perren 1979). Thereafter, endochondral ossification of the cartilage
occurs and bone forms. Finally, the new bone is remodelled and integrated into the
original structure. The mechanical environment is crit occurs and bone forms. Finally, the new bone is remodelled and integrated into the original structure. The mechanical environment is critical to the tissue regeneration.
Fracture immobilization may enhance early healing wh original structure. The mechanical environment is critical to the tissue regeneration.
Fracture immobilization may enhance early healing while stability is critical, but
fractured bones that are dynamically loaded during h Fracture immobilization may enhance early healing while stability is critical, but
fractured bones that are dynamically loaded during healing regain strength more
quickly. However, if the applied strains are too large, car fractured bones that are dynamically loaded during healing regain strength more quickly. However, if the applied strains are too large, cartilage or fibrous tissue forms and a pseudo-joint may develop at the fracture site.

int may develop at the fracture site.
3. Mechanical regulation of bone structure (*a*) *Adaptation experiments*

 (a) Adaptation experiments
The growth and development of organisms living within Earth's gravitational field The growth and development of organisms living within Earth's gravitational field
is intricately linked to mechanical demands. Manipulation of forces in animal exper-
iments has provided insights into the overall nature of The growth and development of organisms living within Earth's gravitational field
is intricately linked to mechanical demands. Manipulation of forces in animal exper-
iments has provided insights into the overall nature of is intricately linked to mechanical demands. Manipulation of forces in animal experiments has provided insights into the overall nature of the adaptation process. The characteristics of adaptation to increased or decreased iments has provided insights into the overall nature of the adaptation process. The characteristics of adaptation to increased or decreased in vivo loading include the following: changes in bone quantity, not material qua characteristics of adaptation to increased or decreased *in vivo* loading include the following: changes in bone quantity, not material quality; greater response in immature than mature tissue; and, response to cyclic, no following: changes in bone quantity, not material quality; greater response in imma-
ture than mature tissue; and, response to cyclic, not static, loading. These results
were elegantly demonstrated in a series of studies b ture than mature tissue; and, response to cyclic, not static, loading. These results
were elegantly demonstrated in a series of studies by Hert *et al.* (1971) with loads
applied to rabbit limbs and have been confirmed by were elegantly demonstrated in a series of studies by Hert *et al.* (1971) with loads applied to rabbit limbs and have been confirmed by a variety of studies. In the adult, in general, when the loads are increased over no applied to rabbit limbs and have been confirmed by a variety of studies. In the adult, in general, when the loads are increased over normal levels, bone mass is increased, and when the loads are decreased, bone mass is los in general, when the loads are increased over normal levels, bone mass is increased, and when the loads are decreased, bone mass is lost. Changes occur in the cross-sectional size and shape of cortical bone and in the appa and when the loads are decreased, bone mass is lost. Changes occur in the cross-
sectional size and shape of cortical bone and in the apparent density of trabeculae;
bone length is seldom significantly affected, but curvat extional size and shape of cortical bone and in the apparent density of trabeculae;
me length is seldom significantly affected, but curvature may be altered.
Most experiments examine cortical bone responses, in contrast to

interest in trabecular adaptation. Exercise studies often show little or no effect, presumably because the overall activity level is not substantially elevated beyond interest in trabecular adaptation. Exercise studies often show little or no effect,
presumably because the overall activity level is not substantially elevated beyond
the normal range. Demonstrating a definitive decrease i presumably because the overall activity level is not substantially elevated beyond
the normal range. Demonstrating a definitive decrease in physiological loads is more
straightforward and has been accomplished by casting, the normal range. Demonstrating a definitive decrease in physiological loads is more straightforward and has been accomplished by casting, space flight and hindlimb suspension. Hindlimb suspension was developed as a ground straightforward and has been accomplished by casting, space flight and hindlimb
suspension. Hindlimb suspension was developed as a ground-based model for space
flight, demonstrating similar skeletal effects. Compared with suspension. Hindlimb suspension was developed as a ground-based model for space flight, demonstrating similar skeletal effects. Compared with age-matched controls,
suspended growing animals continue to grow, but at a reduced rate, with lower age-
related increases in femur strength and cross-sectiona suspended growing animals continue to grow, but at a reduced rate, with lower age-
related increases in femur strength and cross-sectional area (figure 4). van der Meulen
et al. (1995) showed the decreased formation occu related increases in femur strength and cross-sectional area (figure 4). value *et al.* (1995) showed the decreased formation occurs on the outer correxactly the location of the greatest reduction in mechanical stimulus.
W *et al.* (1995) showed the decreased formation occurs on the outer cortical surface, exactly the location of the greatest reduction in mechanical stimulus.
While many experiments have been performed, quantitative relation

While many experiments have been performed, quantitative relationships between have found a remarkable similarity of peak surface strains: $-2000\mu\epsilon$ at the midshaft

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nd cross-sectional area
hindlimb suspension.

hindlimb suspension.

of different bones across different animals at maximum activity (Rubin & Lanyon

1984). Measuring strains in adaptation studies would allow us to relate in vivo load of different bones across different animals at maximum activity (Rubin & Lanyon 1984). Measuring strains in adaptation studies would allow us to relate *in vivo* load changes to altered surface strains to adapted bone mass of different bones across different animals at maximum activity (Rubin 1984). Measuring strains in adaptation studies would allow us to relate changes to altered surface strains to adapted bone mass and strength.
Applying 84). Measuring strains in adaptation studies would allow us to relate *in vivo* load
anges to altered surface strains to adapted bone mass and strength.
Applying loads directly to a skeletal site has the advantage of known

changes to altered surface strains to adapted bone mass and strength.
Applying loads directly to a skeletal site has the advantage of known or controllable
load magnitudes, frequency and duration. Loads at sites or in dire Applying loads directly to a skeletal site has the advantage of known or controllable load magnitudes, frequency and duration. Loads at sites or in directions that are not normally loaded have been demonstrated to induce a ing physiological loads. Recent experimental models for non-invasive, controlled *in vivo* loaded have been demonstrated to induce a greater response than increasing physiological loads. Recent experimental models for non-invasive, controlled *in vivo* loading have been developed for weight-bearing bone *vivo* loading have been developed for weight-bearing bones in the rat (Turner *et al.* 1991; Torrance *et al.* 1994). The latter group is one of the few that has integrated these *in vivo* approaches with *in vitro* and 1991; Torrance *et al.* 1994). The latter group is one of the few that has integrated these *in vivo* approaches with *in vitro* and *ex vivo* studies to acquire a more complete understanding of load-induced adaptation. T these *in vivo* approaches with *in vitro* and *ex vivo* studies to acquire a more com-
plete understanding of load-induced adaptation. These animal models can be used
to examine loading parameters, to study gene expressio plete understanding of load-induced adaptation. These animal models can be used
to examine loading parameters, to study gene expression, and to validate computer
simulations. The mouse has recently become more relevant; ou to examine loading parameters, to study gene expression, and to validate computer
simulations. The mouse has recently become more relevant; our ability to manipu-
late the mouse genome has led to the development of mutati simulations. The mouse has recently become more relevant; our ability to manipulate the mouse genome has led to the development of mutations and new biological markers and assays. *In vivo* loading of mouse mutants will he late the mouse genome has led to the development of mutations and new biological markers and assays. In vivo loading of mouse mutants will help identify critical genes and regulatory factors in the mechanical response pat Framework and assays. In vivo loading of mouse mutants will help identify critical geness dependincy factors in the mechanical response pathway.
Adaptation around bone implants has received considerable attention clinical

and regulatory factors in the mechanical response pathway.
Adaptation around bone implants has received considerable attention clinically
and experimentally. When a bone segment is replaced by a stiff metal prosthesis,
the Adaptation around bone implants has received considerable attention clinically
and experimentally. When a bone segment is replaced by a stiff metal prosthesis,
the implant becomes the primary load bearing structure, reduci and experimentally. When a bone segment is replaced by a stiff metal prosthesis, the implant becomes the primary load bearing structure, reducing the mechanical stimulus to the surrounding bone. Severe bone loss is one of the implant becomes the primary load bearing structure, reducing the mechanical
stimulus to the surrounding bone. Severe bone loss is one of the impediments to
the long-term success of orthopaedic joint replacements. Futur stimulus to the surrounding bone. Severe bone loss is one of the impediments to
the long-term success of orthopaedic joint replacements. Future developments will
include active devices that stimulate the surrounding bone a the long-term success of orthopaedic
include active devices that stimulate t
organs engineered in the laboratory.

(*b*) *Modelling*

For a skeletal element to respond to its mechanical environment, the cells within For a skeletal element to respond to its mechanical environment, the cells within
the tissue must regulate their environment in response to the mechanical stimuli
they receive. The regulatory process can be thought of as For a skeletal element to respond to its mechanical environment, the cells within
the tissue must regulate their environment in response to the mechanical stimuli
they receive. The regulatory process can be thought of as a the tissue must regulate their environment in response to the mechanical stimuli
they receive. The regulatory process can be thought of as a feedback loop (figure 5),
where the osteocyte senses the stimulus and signals the they receive. The regulatory process can be thought of as a feedback loop (figure 5), where the osteocyte senses the stimulus and signals the osteoclasts and osteoclasts to either add or resorb tissue to regain the requir where the osteocyte senses the stimulus and signals the osteoblasts and osteoclasts
to either add or resorb tissue to regain the required physiological environment for
the cell. We can define a homeostatic mechanical stim to either add or resorb tissue to regain the required physiological environment for the cell. We can define a homeostatic mechanical stimulus, S_0 , necessary to maintain bone density. Then, if the tissue should be subje bone density. Then, if the tissue should be subjected to any other stimulus, S, there
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Figure 5. Feedback diagram for skeletal mechanical regulation.

will be a driving signal to adapt the tissue to re-establish the homeostatic equilibrium. The simplest mathematical model for such a mechano-regulatory process is given by

$$
\frac{\mathrm{d}M}{\mathrm{d}t} = C(S - S_0),\tag{3.1}
$$

 $\frac{dS}{dt} = C(S - S_0),$ (3.1)
where *M* is the mass of the element, *C* is a rate constant, and $(S - S_0)$ is the
driving signal. Since the sensory cells are distributed throughout the tissue this where M is the mass of the element, C is a rate constant, and $(S - S_0)$ is the driving signal. Since the sensory cells are distributed throughout the tissue, this model describes a spatially discrete process: each cell wil where M is the mass of the element, C is a rate constant, and $(S - S_0)$ is the driving signal. Since the sensory cells are distributed throughout the tissue, this model describes a spatially discrete process: each cell wil driving signal. Since the sensory cells are distributed throughout the tissue, this model describes a spatially discrete process: each cell will regulate its stimuli by changing the mass or density of its extracellular en model describes a spatially discrete process: each cell will regulate its stimuli by changing the mass or density of its extracellular environment. Many biomechanical stimuli have been proposed, including strain (Cowin & changing the mass or density of its extracellular environment. Many biomechanical
stimuli have been proposed, including strain (Cowin & Hegedus 1976), strain energy
density (Carter *et al.* 1987; Huiskes *et al.* 1987) or stimuli have been proposed, including strain (Cowin & Hegedus 1976), strain energy
density (Carter *et al.* 1987; Huiskes *et al.* 1987) or fatigue microdamage (Prender-
gast & Taylor 1994). These approaches were first co density (Carter *et al.* 1987; Huiskes *et al.* 1987) or fatigue microdamage (Prendergast & Taylor 1994). These approaches were first coupled to computational stress analysis procedures by Hart *et al.* (1984) and are capa gast & Taylor 1994). These approaches were first coupled to computational stress
analysis procedures by Hart *et al.* (1984) and are capable of predicting bone adap-
tation around implants (van Rietbergen *et al.* 1993) a analysis procedures by Hart *et al.* (1984) and are capable of protation around implants (van Rietbergen *et al.* 1993) and simulate mechanics on long bone growth (van der Meulen *et al.* 1993).
Recently considerable inter tion around implants (van Rietbergen *et al.* 1993) and simulating the influence of echanics on long bone growth (van der Meulen *et al.* 1993).
Recently, considerable interest has been given to investigations of the nonl

mechanics on long bone growth (van der Meulen *et al.* 1993).
Recently, considerable interest has been given to investigations of the nonlinear
dynamics of bone adaptation. Finite-element models have been used in iterative Recently, considerable interest has been given to investigations of the nonlinear dynamics of bone adaptation. Finite-element models have been used in iterative computer simulation procedures (Carter *et al.* 1989; Weinans *dynamics* of bone adaptation. Finite-element models have been used in iterative computer simulation procedures (Carter *et al.* 1989; Weinans *et al.* 1992; Jacobs *et al.* 1995). To illustrate the dynamics of achieving a computer simulation procedures (Carter *et al.* 1989; Weinans *et al.* 1992; Jacobs *et al.* 1995). To illustrate the dynamics of achieving a homeostatic equilibrium, we can consider a beam of bone in three-point bending. al. 1995). To illustrate the dynamics of achieving a homeostatic equilibrium, we can consider a beam of bone in three-point bending. If we choose strain energy per unit mass to be the mechanical stimulus, then $S = U/\rho$, wh consider a beam of bone in three-point bending. If we choose strain energy per unit
mass to be the mechanical stimulus, then $S = U/\rho$, where U is the strain energy
density and ρ is the apparent density. Starting with so mass to be the mechanical stimulus, then $S = U/\rho$, where U is the strain energy
density and ρ is the apparent density. Starting with some initial density pattern,
the evolution of density can be determined using the kno density and ρ is the apparent density. Starting with some initial density pattern,
the evolution of density can be determined using the known relationship between
density and modulus. To obtain a mesh independent solut the evolution of density can be determined using the known relationship between
density and modulus. To obtain a mesh independent solution for equation (3.1) , one
approach is to integrate the stimulus over an influence

$$
\frac{dM_j}{dt} = B \sum_{i=1}^{n} f_{ij}(S - S_0),
$$
\n(3.2)

where M_j is the mass at position j, B is a rate constant and f_{ij} is a spatial influ-
ence function that incorporates the stimulus at position *i* into the change of mass where M_j is the mass at position j, B is a rate constant and f_{ij} is a spatial influ-
ence function that incorporates the stimulus at position i into the change of mass
at position i (Mullender & Huiskes 1995) If a un where M_j is the mass at position j, B is a rate constant and f_{ij} is a spatial influ-
ence function that incorporates the stimulus at position i into the change of mass
at position j (Mullender & Huiskes 1995). If a u ence function that incorporates the stimulus at position i into the change of mass
at position j (Mullender $\&$ Huiskes 1995). If a uniform initial density is taken, the
simulation proceeds by each element adapting i at position j (Mullender & Huiskes 1995). If a uniform initial density is taken, the simulation proceeds by each element adapting independently; some elements will resorb to zero density and others will achieve the maximu simulation proceeds by each element adapting independently; some elements will
resorb to zero density and others will achieve the maximum density and the homeo-
static equilibrium is a porous 'trabecular' structure, see fi resorb to zero density and others will achieve the maximum density and the homeo-
static equilibrium is a porous 'trabecular' structure, see figure $6a$. This phenomenon
can be viewed as a self-organizational process oper

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(*b*) (*c*)
Figure 6. Adaptation of a bone beam subjected to three-point bending, (*a*) starting from a uniform density (*h*) starting from a non-uniform density and (*c*) adaptation of structure shown Figure 6. Adaptation of a bone beam subjected to three-point bending, (a) starting from a uniform density, (b) starting from a non-uniform density, and (c) adaptation of structure shown in (a) after fracture of a trab uniform density, (b) starting from a non-uniform density, and (c) adaptation of structure shown
in (a) after fracture of a trabecula. Courtesy of Dr Ir. Harrie Weinans, Erasmus Universiteit Rotterdam.

et al. 1992). A different initial density pattern will lead to a different trabecular et al. 1992). A different initial density pattern will lead to a different trabecular structure (figure 6*b*), illustrating the nonlinear nature of the adaptation process.
Furthermore, the homeostatic equilibria, or end-co *et al.* 1992). A different initial density pattern will lead to a different trabecular structure (figure 6b), illustrating the nonlinear nature of the adaptation process. Furthermore, the homeostatic equilibria, or end-c structure (figure $6b$), illustrating the nonlinear nature of the adaptation process.
Furthermore, the homeostatic equilibria, or end-configurations, may be considered
metastable because a perturbation of the structure ca Furthermore, the homeostatic equilibria, or end-configurations, may be considered metastable because a perturbation of the structure caused by the fracture of a trabecula, for example, will not be followed by a return to t metastable because a perturbation of the structure caused by the fracture of a trabecula, for example, will not be followed by a return to the former equilibrium. However, bone structures are stable in the sense that the i ula, for example, will not be followed by a return to the former equilibrium. However,
bone structures are stable in the sense that the inevitable trabecular microfractures
that occur in aged osteoporotic bone do not lead bone structures are stable in the sense that the inevitable trabecular microfractures
that occur in aged osteoporotic bone do not lead to immediate degeneration, rather
a completely new equilibrium is sought by the regulat that occur in aged osteoporotic bone do not lead to immediate degeneration, rather
a completely new equilibrium is sought by the regulatory process; the structure is
almost immediately trapped in another metastable equilib a completely new equilibrium is sought by the regulatory process; the structure is
almost immediately trapped in another metastable equilibrium (figure $6c$). If this
computer simulation does indeed capture the essence of almost immediately trapped in another metastable equilibrium (figure $6c$). If this computer simulation does indeed capture the essence of bone adaptation, then adaptation is a far-from-equilibrium process generated by po computer simulation does indeed capture the essence of bone adaptation, then adaptation is a far-from-equilibrium process generated by positive feedback whereby elements of tissue compete for mechanical stimulus (Weinans & tation is a far-from-equilibrium process generated by positive feedback whereby elements of tissue compete for mechanical stimulus (Weinans $\&$ Prendergast 1996). To date, these approaches have focused attention on the c ments of tissue compete for mechanica
To date, these approaches have focused
factors in determining bone structure.
Mechano-biologic concepts have been To date, these approaches have focused attention on the central role of mechanical factors in determining bone structure.
Mechano-biologic concepts have been applied to other skeletal tissues. Differen-

factors in determining bone structure.
Mechano-biologic concepts have been applied to other skeletal tissues. Differen-
tiation of stem cells to form cartilage, fibrous tissue and bone is central to tissue
growth and regen Mechano-biologic concepts have been applied to other skeletal tissues. Differentiation of stem cells to form cartilage, fibrous tissue and bone is central to tissue growth and regeneration. Pauwels (1941) proposed that hyd tiation of stem cells to form cartilage, fibrous tissue and bone is central to tissue
growth and regeneration. Pauwels (1941) proposed that hydrostatic stresses stim-
ulate differentiation to cartilage cells, whereas disto growth and regeneration. Pauwels (1941) proposed that hydrostatic stresses stimulate differentiation to cartilage cells, whereas distortion stimulates differentiation into fibrous cells (figure 3). Simulations based on Pau patterns of mechanical stimuli with tissue type during fracture healing (Carter *et* into fibrous cells (figure 3). Simulations based on Pauwels's ideas have correlated patterns of mechanical stimuli with tissue type during fracture healing (Carter *et al.* 1998). These models suggest that we will be able patterns of mechanical stimuli with tissue type during frace al. 1998). These models suggest that we will be able to si
adaptation and degeneration over an individual's lifetime.

(*c*) *Imaging*

A key new tool in the validation of analytical models is high resolution imaging E σ maying
A key new tool in the validation of analytical models is high resolution imaging
coupled with computer analyses to calculate the material stresses, strains and stimuli
within cancellous bone. The average thi A key new tool in the validation of analytical models is high resolution imaging
coupled with computer analyses to calculate the material stresses, strains and stimuli
within cancellous bone. The average thickness of a tr coupled with computer analyses to calculate the material stresses, strains and stimuli
within cancellous bone. The average thickness of a trabecula is $100{-}150 \mu m$, unde-
tectable with conventional computed tomography re within cancellous bone. The average thickness of a trabecula is $100-150 \mu m$, undetectable with conventional computed tomography resolution of $100-200 \mu m$. Microcomputed tomography (microCT) can currently image bone at computed tomography (microCT) can currently image bone at $17 \mu m$ resolution, and the images can be converted directly into large-scale, finite-element models (figure 7). These models can determine bone stiffness and strength without the need for a trathe images can be converted directly into large-scale, finite-element models (figure 7).
These models can determine bone stiffness and strength without the need for a tra-
ditional mechanical test. These 'virtual bone biop These models can determine bone stiffness and strength without the need for a tra-
ditional mechanical test. These 'virtual bone biopsies' (Müller & Rüegsegger 1995)
have the potential to revolutionize the clinical assess ditional mechanical test. These 'virtual bone biopsies' (Müller & Rüegsegger 1995) have the potential to revolutionize the clinical assessment of bone health, an increasingly important clinical objective in an ageing popu *Phil. Trans. R. Soc. Lond.* A (2000)

⁵⁷⁴ *M. C. H. [van der Meulen and P. J](http://rsta.royalsocietypublishing.org/). Prendergast* Downloaded from rsta.royalsocietypublishing.org

Figure 7. A finite-element model of a cancellous bone specimen generated using microCT scanning. The distribution of tissue level stresses is computed for compression.

Sanning. The distribution of tissue level stresses is computed for compression.
Although these microCT-based models simulate the architecture precisely, the mag-
nitude and variation of tissue-level material properties sti Although these microCT-based models simulate the architecture precisely, the magnitude and variation of tissue-level material properties still needs to be determined.
Another imaging development is laser scanning confocal nitude and variation of tissue-level material properties still needs to be determined.
Another imaging development is laser scanning confocal microscopy (LSCM) to

indude and variation of tissue-level material properties still needs to be determined.
Another imaging development is laser scanning confocal microscopy (LSCM) to
image individual living cells non-invasively. The deformati Another imaging development is laser scanning confocal microscopy (LSCM) to image individual living cells non-invasively. The deformation of osteoblasts and chondrocytes has been observed using this method (see, for exampl drocytes has been observed using this method (see, for example, Boyde *et al.* 1995; Guilak *et al.* 1995). LSCM has also been used to image microdamage in bone tissue drocytes has been observed using this method (see, for example, Boyde *et al.* 1995;
Guilak *et al.* 1995). LSCM has also been used to image microdamage in bone tissue
(see, for example, Zioupos *et al.* 1994) showing mode Guilak *et al.* 1995). LSCM has also been use (see, for example, Zioupos *et al.* 1994) show the complex microstructure of bone tissue. the complex microstructure of bone tissue.
4. Visions for the future

With these new tools and so many unanswered questions about tissue function and maintenance, the time for mechano-biology has truly arrived. High-resolution imag-With these new tools and so many unanswered questions about tissue function and
maintenance, the time for mechano-biology has truly arrived. High-resolution imag-
ing systems will allow tissue structures to be determined f maintenance, the time for mechano-biology has truly arrived. High-resolution imaging systems will allow tissue structures to be determined from the highest hierarchy of the organ to the lowest of the genome. These digital ing systems will allow tissue structures to be determined from the highest hierarchy
of the organ to the lowest of the genome. These digital images are ideally suited for
analysing physical forces and linking continuum lev of the organ to the lowest of the genome. These digital images are ideally suited for analysing physical forces and linking continuum level tissue stresses to deformation-
induced gene activation in the DNA molecule. Advan analysing physical forces and linking continuum level tissue stresses to deformation-
induced gene activation in the DNA molecule. Advances in dynamic systems theory
and applied mathematics will play a critical role in exp induced gene activation in t
and applied mathematics wi
erwise intractable models.
As the complete genomes d applied mathematics will play a critical role in explaining the behaviour of oth-
wise intractable models.
As the complete genomes of organisms become mapped, functional genomics will
mbine with biomechanics to answer qu

erwise intractable models.
As the complete genomes of organisms become mapped, functional genomics will
combine with biomechanics to answer questions such as: What is the regulatory
role of mechanics in skeletal gene expre As the complete genomes of organisms become mapped, functional genomics will
combine with biomechanics to answer questions such as: What is the regulatory
role of mechanics in skeletal gene expression? How would organisms combine with biomechanics to answer questions such as: What is the regulatory role of mechanics in skeletal gene expression? How would organisms grow in the microgravity environment of space? Can we define the mechanical f role of mechanics in skeletal gene expression? How would organisms grow in the microgravity environment of space? Can we define the mechanical forces needed to culture complete skeletal organs in the laboratory? Are there microgravity environment of space? Can we define the mechanical forces needed to culture complete skeletal organs in the laboratory? Are there genes that code for 'bone strength' ? Orthopaedics and reconstructive surgery w tionized. The following the rapid growth of the field has produced an interdisciplinary community of engi-
The rapid growth of the field has produced an interdisciplinary community of engi-

tionized.
The rapid growth of the field has produced an interdisciplinary community of engi-
neers, biologists, mathematicians and physicians with visions of answering scientific
questions of the highest import. These ques The rapid growth of the field has produced an interdisciplinary community of engineers, biologists, mathematicians and physicians with visions of answering scientific questions of the highest import. These questions will b *Phil. Trans. R. Soc. Lond.* A (2000)

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physics and biology, between forces and cells, to understand how organic forms are physics and biology, between forces and cells, to understand how organic forms are shaped by the mechanical world and how living systems actually 'extract order from their environment', first posed by Erwin Schrödinger (19 physics and biology, between forces and cells, to understand how organic forms are shaped by the mechanical world and how living systems actually 'extract order from their environment', first posed by Erwin Schrödinger (19 *What is life?* What is $life$?
We gratefully acknowledge support from the Wellcome Trust for a Biomedical Collaboration

We gratefully acknowledge support from the Wellcome Trust for a Biomedical Collaboration
Grant between Trinity College Dublin and Cornell University, the High Performance Computing
initiative (TCD) and the National Institu We gratefully acknowledge support from the Wellcome Trust for a Bio
Grant between Trinity College Dublin and Cornell University, the High Pe
initiative (TCD), and the National Institutes of Health, NIAMS (CU).

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**MATHEMATICAL,
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