# *Bioactive Bone Cements – Advantages and Limitations*

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UNIVERSITY of LIMERICK

CABER

HEA

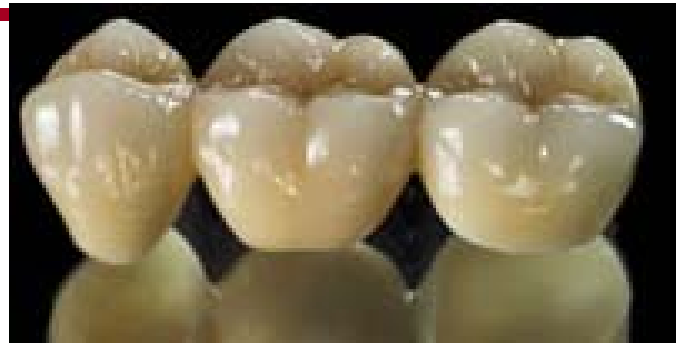
Higher Education Authority
An tÚdarás um Ard-Oideachas

MSSI

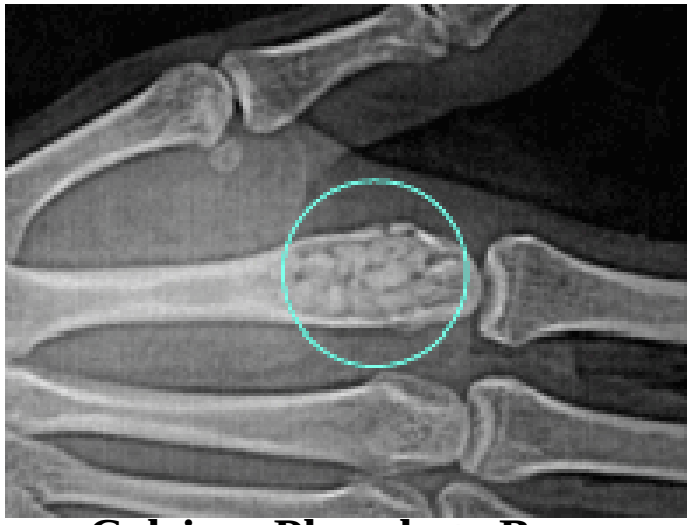
# Ceramics for Biomedical Applications

Alumina on Alumina Hip Bearing

Various ceramic implants

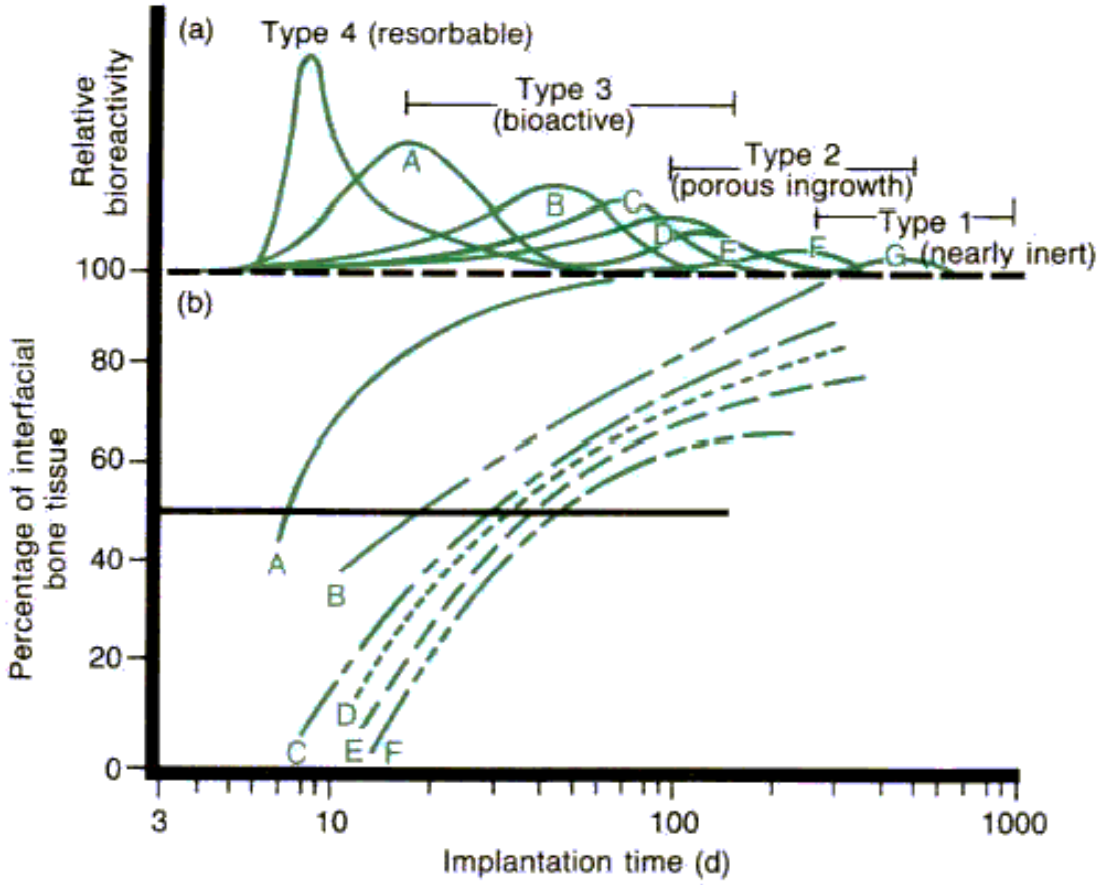


Dental Restoratives



Calcium Phosphate Bone Substitute

# Ceramics of Implant Use




**Bioactivity spectrum for various bioceramic implants, (A) Relative rate of bioreactivity, (B) Time dependence of formation of bone bonding at an implant interface.** [1]


1. Hench, L J. Am. Ceram. Soc. 74 (7) 1487-510 (1991)

# Bioactive Material

- ‘‘one which has been designed to induce specific biological activity’’ [2]
- “Bone bonding….. via a time-dependent, kinetic modification of the surface that occurs upon implantation the surface forms a biologically active hydroxycarbonate apatite (HCA) layer which provides the bonding interface with tissues[1]
- ‘‘.the essential requirement for a material to bond to living bone is the formation of bone-like apatite on its surface when implanted …..this in vivo apatite formation can be reproduced in a simulated body fluid (SBF) with ion concentrations nearly equal to those of human blood
- plasma.’[3]


1. Hench, L J. Am. Ceram. Soc. 74 (7) 1487-510 (1991)
2. ESB consensus conference of 1987.
3. Kokubo T, Takadama H. How useful is SBF in predicting in vivo bone bioactivity? Biomaterials 2006;27:2907–15.

# “Can bioactivity be tested in vitro with SBF solution?”[4]

- “Both serum and SBF are supersaturated towards apatite crystals….. system is metastable and will eventually become thermodynamically stable by forming apatite crystals”

- “Bioactivity testing with SBF may lead not only to false positive but also to false negative results”

- “The use of an in vitro protocol for testing the bone bonding potential of a material remains a very attractive concept and should be contemplated very carefully”

4. Marc Bohner, Jacques Lemaitre Biomaterials 30 (2009) 2175–2179

# Bioactive Bone Cements

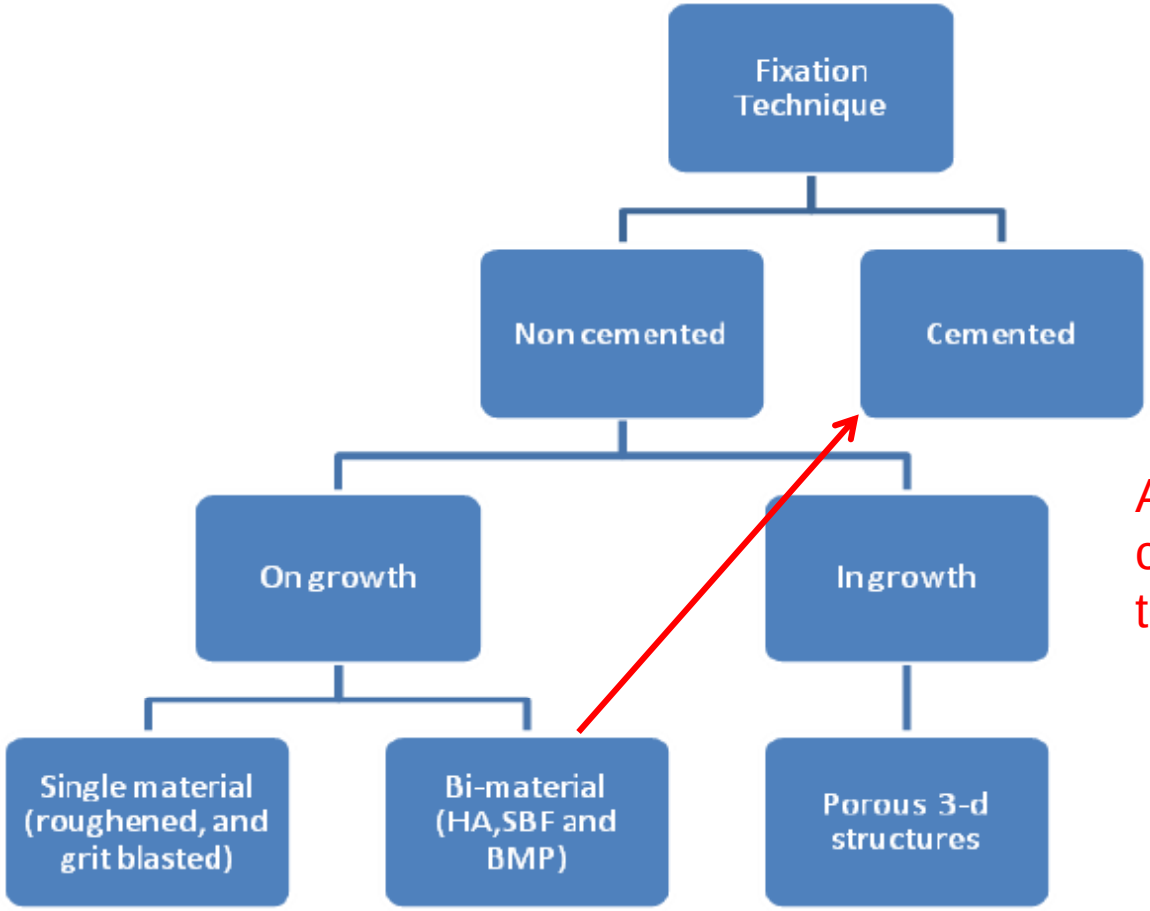
**Bone “Cement” differentiated from Bone “Substitute”**

**Implies:**

- In situ setting – takes up form of individual defect
- Load bearing
- Adhesive (Necessary for stress transmission)
- Bioactive
- Fixation of other devices (Metal/Ceramic/Polymer)

Mutually Exclusive for high strength (density) ceramics

# Fixation of Orthopaedic Devices




Add Bioactive components to cement

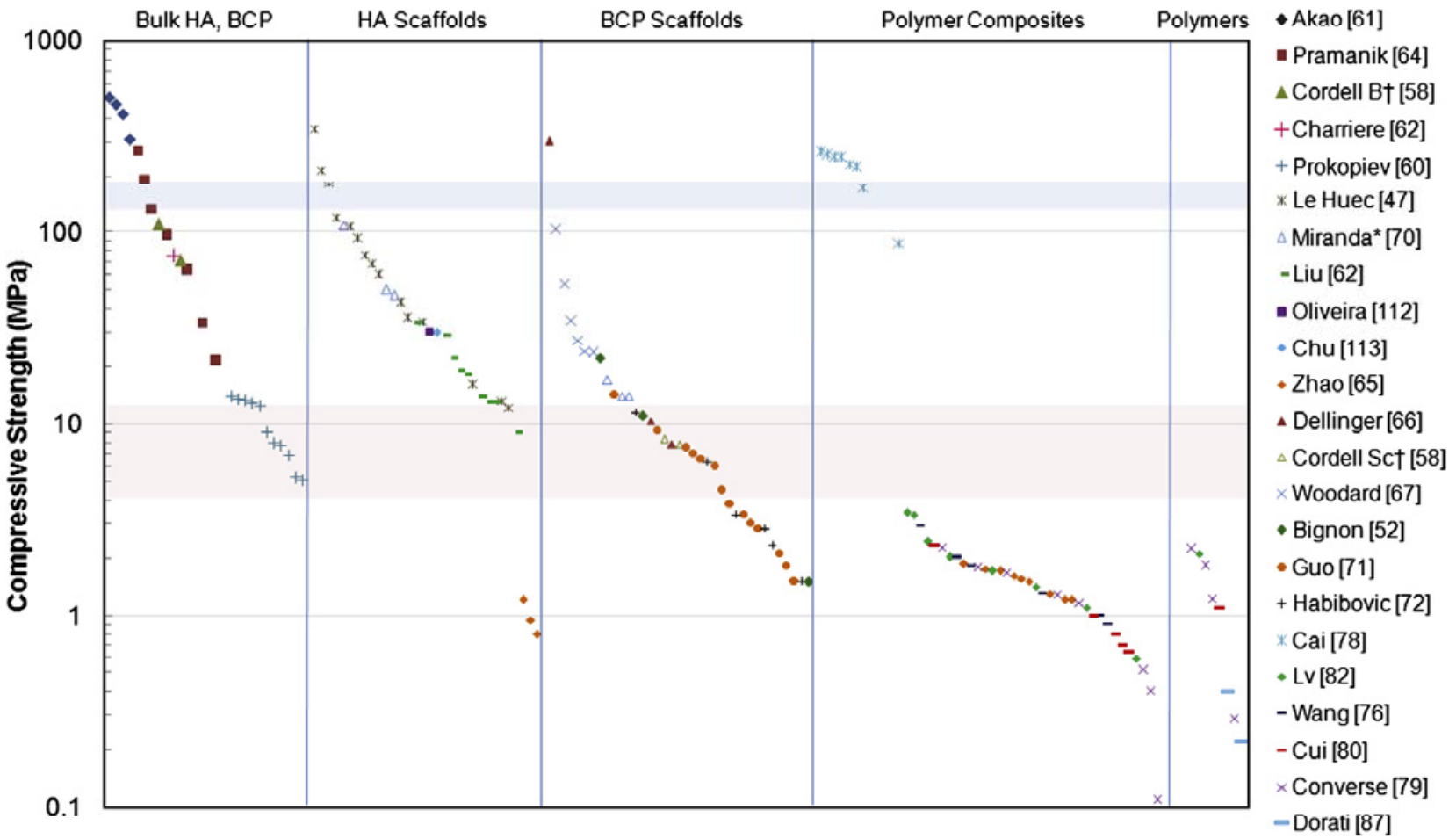
# Design Criteria for Orthopaedic Bone Cement

- Ease of Placement and Handling
- Chemical Adhesion - Hydrophyllic
- Modulus Match with Bone
- Non-cytotoxic (no foreign body response)
- Bioactive ( Osteoconductive / Osteoinductive)
- If resorption required – match regeneration rate
- Rapid Setting
- Dimensionally Stable
- Radiopaque
- Suitable Matrix for drug delivery
- Mechanical & Fracture Properties similar to bone at target site

# Bone Cement Mechanical & Fracture Properties

- Ceramic properties can be characterised as:
  - brittle (low fracture resistance, flaw tolerance)
  - low tensile strength (fibers are exception)
  - poor fatigue resistance (relates to flaw tolerance)
- Bone characterised as:
  - Composite in nature (>5 orders of magnitude in length scale)
  - Variable dependant on site and orientation
  - Viscoelastic
  - Poor fatigue resistance (but built-in repair mechanisms)
- Implies ideal bone cement should be composite (Biomimetic)

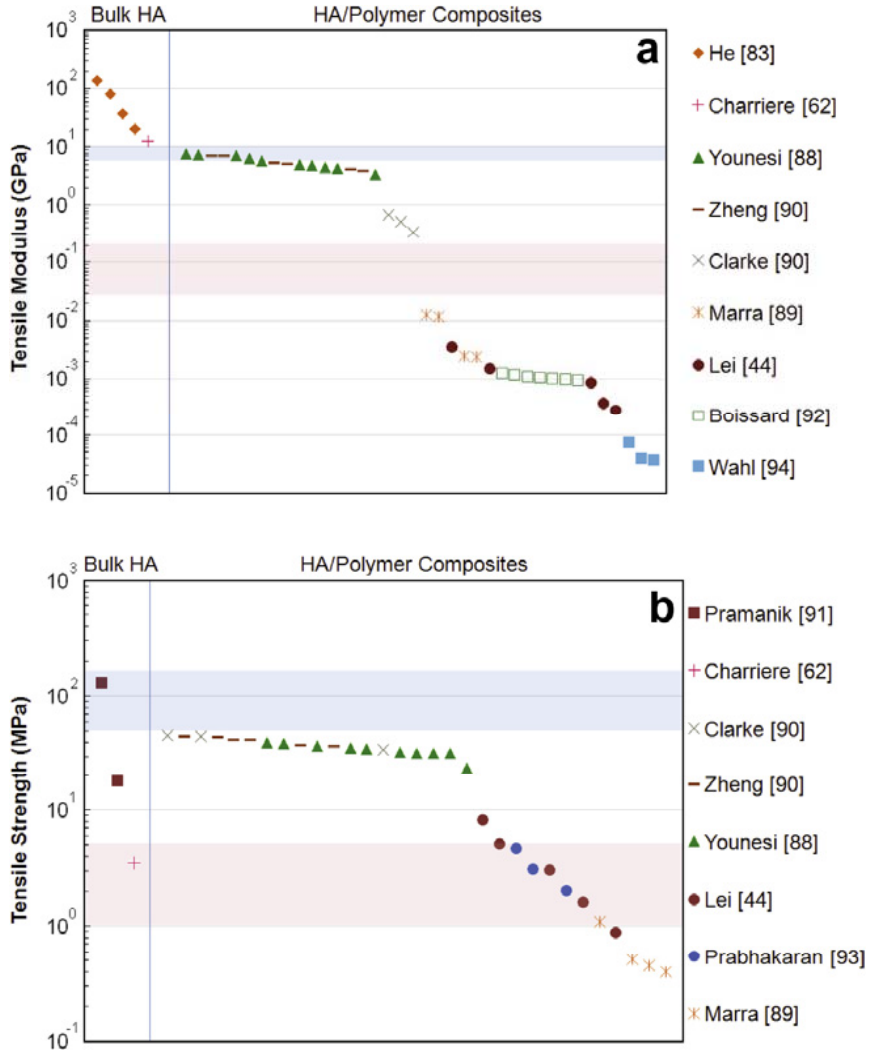
# Compressive Strength of Bio-ceramics, Composites and Polymers [6]



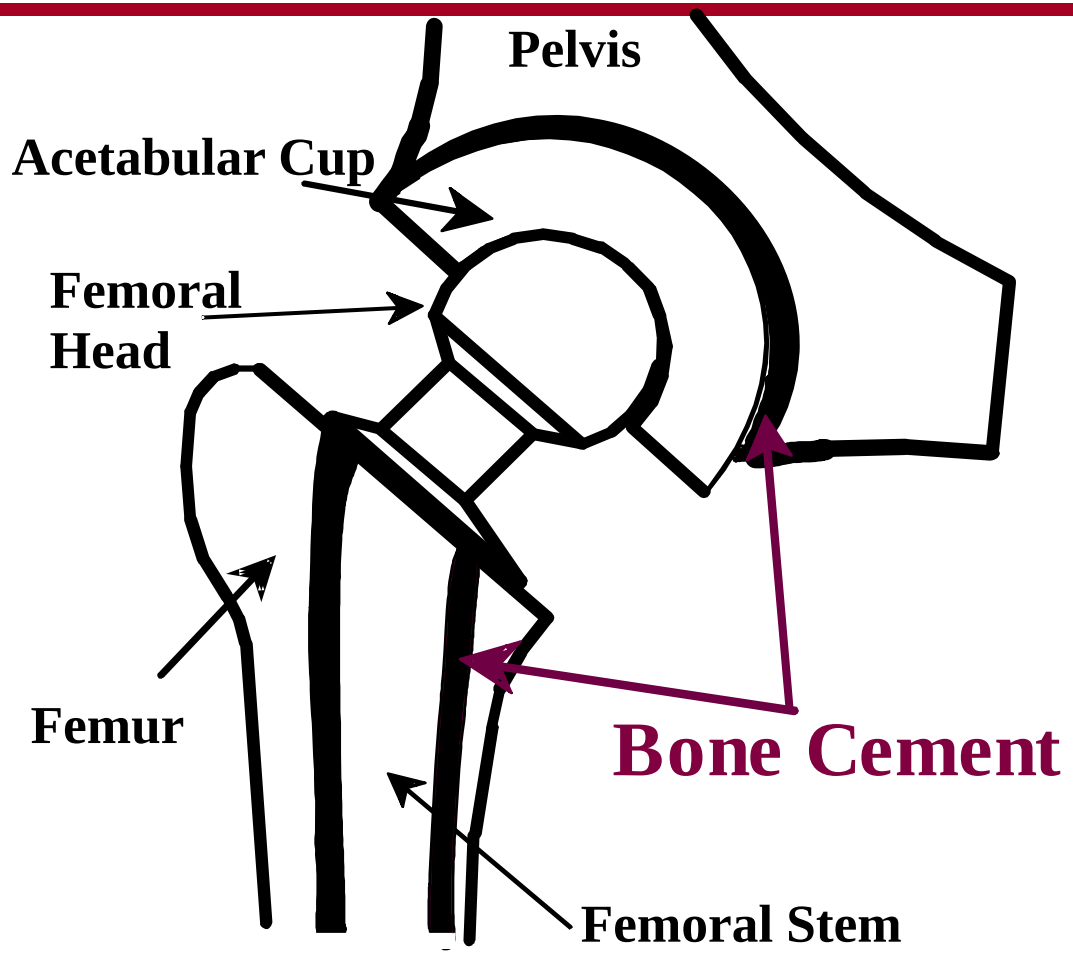



6. Amy J. Wagoner Johnson *, Brad A. Herschler Acta Biomaterialia 7 (2011) 16–30.

# Tensile Modulus and Strength of Bio-ceramics, Composites and Polymers [6]



# BONE CEMENTS




in TOTAL JOINT REPLACEMENTS

# PMMA Bone cement

2-component system: powder and liquid mixed 2:1

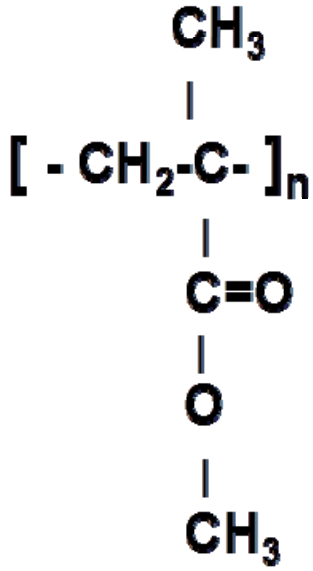
Powder

- PMMA/PMA/PS spheres 30-150um (>90%)
- Radiopacifiers ($BaSO_4$ /$ZrO_2$) ( 4-30%)
- Initiator (benzoyl peroxide) (2-3%)

Liquid

- MMA monomer (>85%)
- Co-monomers (10-15%)
- Inhibitor

Activator (Dimethyl-p –toluidine) (2-3%)




- Mix components together to a doughy stage
- Injected into prepared site, and allowed to cure via free radical polymerisation

# Intraoperative Complications

- Nerve Injury
- Vascular Injury
- Cement Reaction/Fat Embolus
- Fracture/Canal Perforation

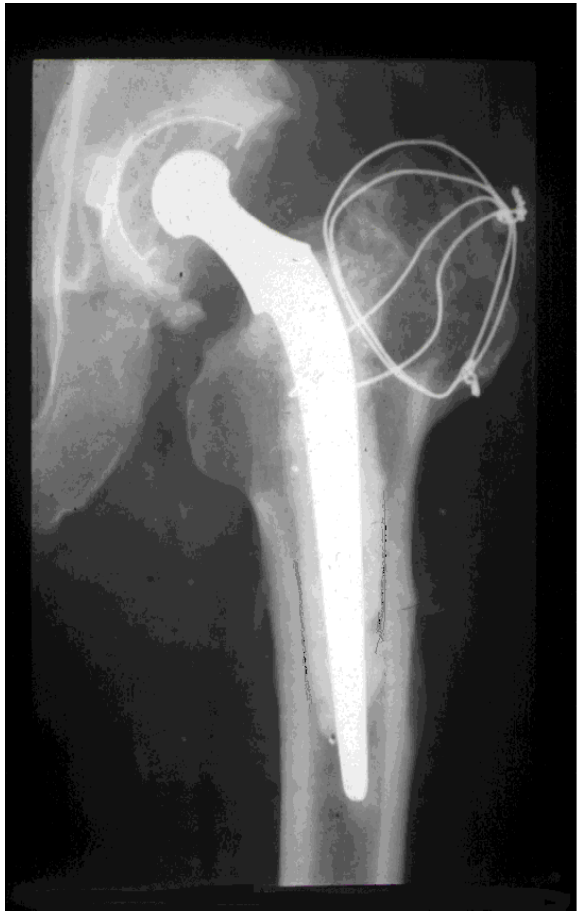
# Post-Operative Complications

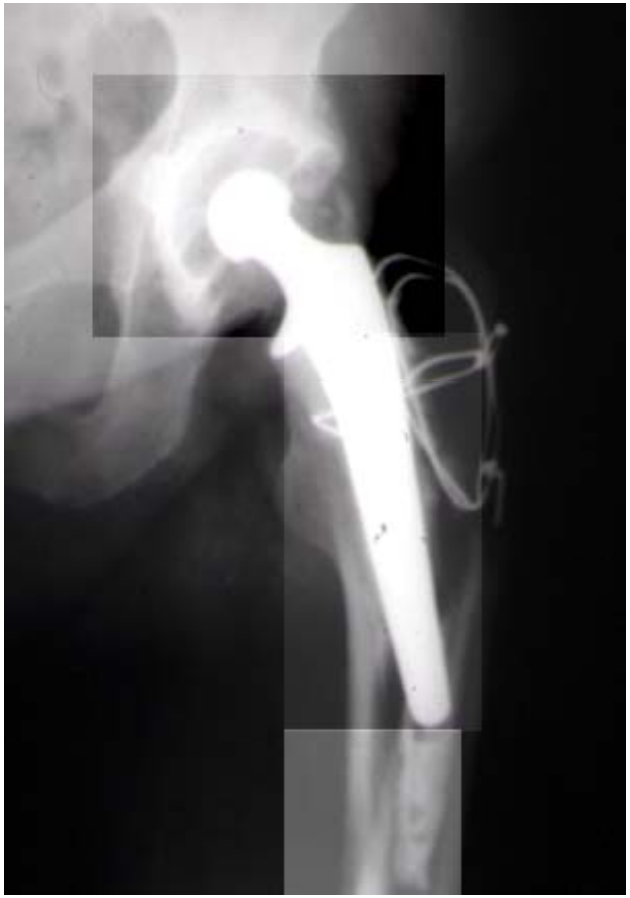
- Fracture
- Instability
- Heterotopic Ossification
- Aseptic Loosening
- Sepsis
- Venous Thrombosis
- Implant Wear and Failure

# Causes for Revision (Mayo Clinic)

1. Aeseptic Loosening
2. Fracture
3. Dislocation
4. Infection

# Aeseptic Loosening

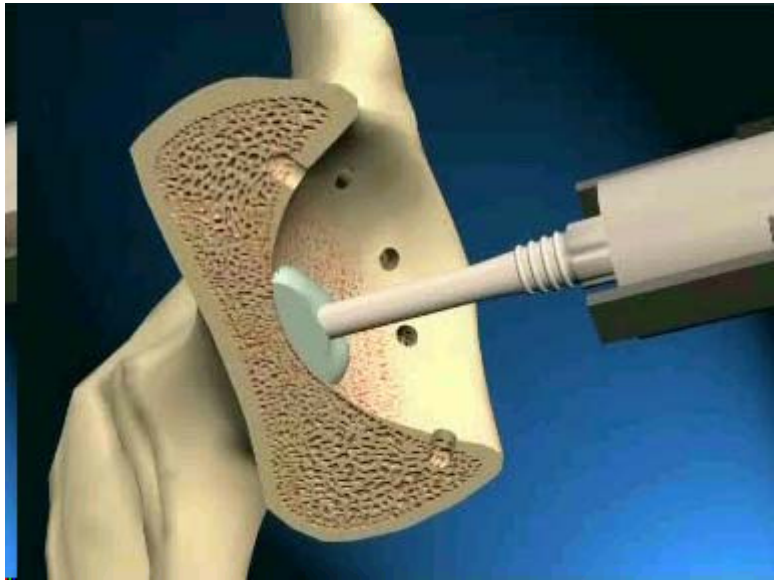




**Note the formation of a radiolucent layer as a result of fibrous capsule layer and stress shielding that leads to failure.**

# Contributions to Aseptic Loosening:

- Complex aetiology.
- No chemical bond.
- Thermal Necrosis.
- Chemical necrosis.
- Osteolysis



- Stress shielding –due to modulus mismatch.
- Shrinkage –up to 22%.

# Properties Vs Design Criteria

| Properties | PMMA bone cements |
|---|---|
| Quick setting (3 to 15 minutes) | Yes |
| Exotherm < 56° C | No |
| Matrix for drug delivery | No |
| Osteointegrative (promotes bone growth) | No |
| Bioactive | if Bioactive ingredient added |
| Bioresorbable | No |
| Adequate viscosity | Yes |
| Radio-opaque | Yes if $BaSO_4$ or $ZrO_2$ is added |
| Modulus match with trabecular bone (~10-20 MPa) | No |
| Adhesive bond formation with bone/implant | No |
| Dimensional stability | No |
| • Fibrous encapsulation | |
| • Local toxicity monomer | |
| • Systemic toxicity –cardiovascular, liver & immune impairment | |

# Bioactive Resin Composite- Cortoss™

**Di-functional Monomers**

- bisGMA
- bisEMA
- TEGDM

**Reinforcing / Bioactive Fillers**

- 45S5 Glass Ceramic (Combeite crystalline phase)
- Barium-Borosilicate glass

**Activator + Initiator**

- BPO
- DMPT

# Bioactive Resin VCF Composite- Cortoss™

**Di-functional Monomers**

- Cross-linked Network – increased stiffness
- high degree of monomer conversion, lower exotherm-63$^0$C
- Higher Mw than MMA - decreased leachable toxic monomer

**Reinforced with ceramic particles**

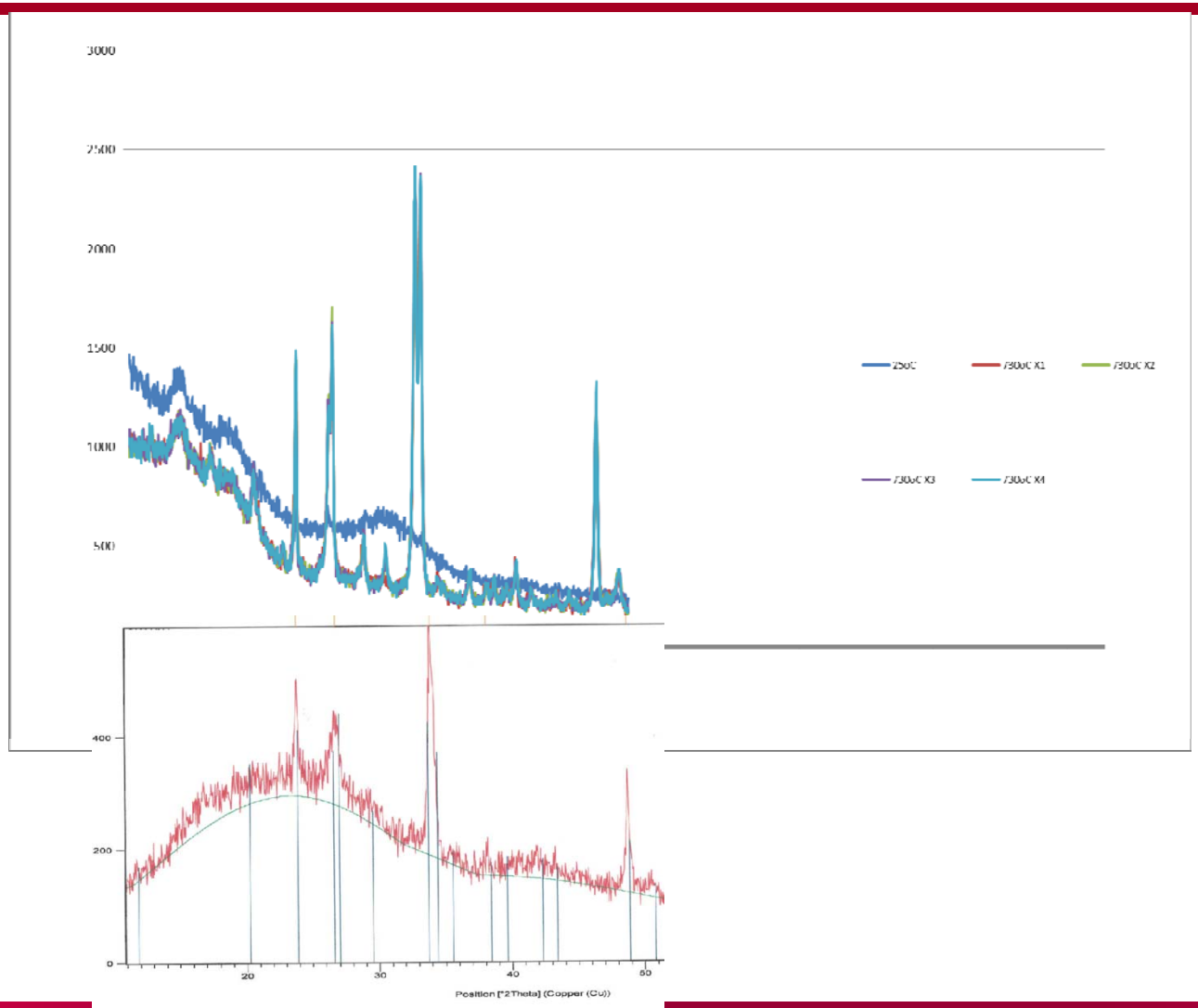
- increased stiffness

**Bioactive Components**

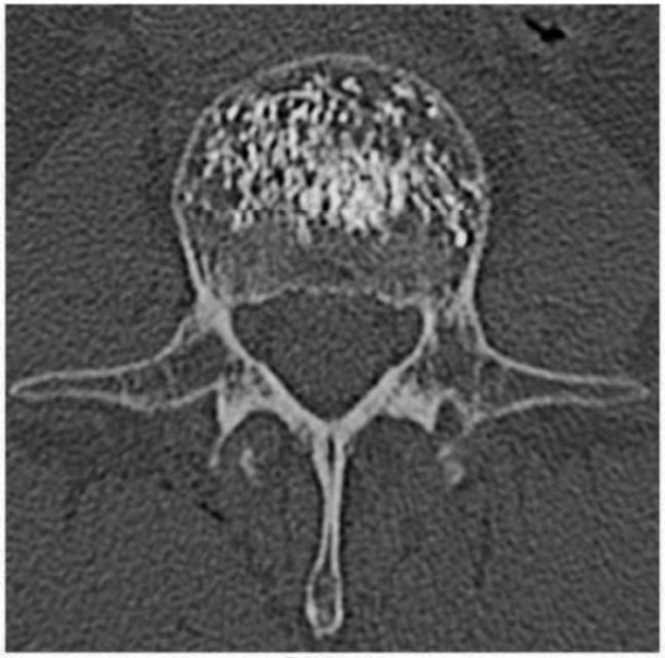
- Increased bone apposition at the interface
- Improved interfacial bond strengths between implant and bone


1. G.J. Pomrink, M.P. Dicicco, T.D. Clineff, E.M. Erbe, Biomaterials 24, 1023 (2003)
2. E.M. Erbe, T.D. Clineff, G. Gualtieri, Eur. Spine J. 10, S147 (2001)

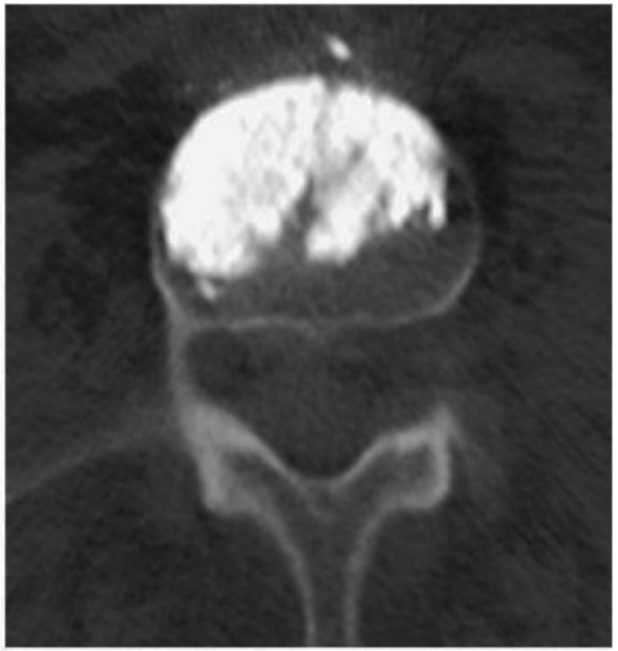
# Cortoss™ Mechanical Property Comparison



# Cortoss™ Dispersed Fill of Vertebral Body



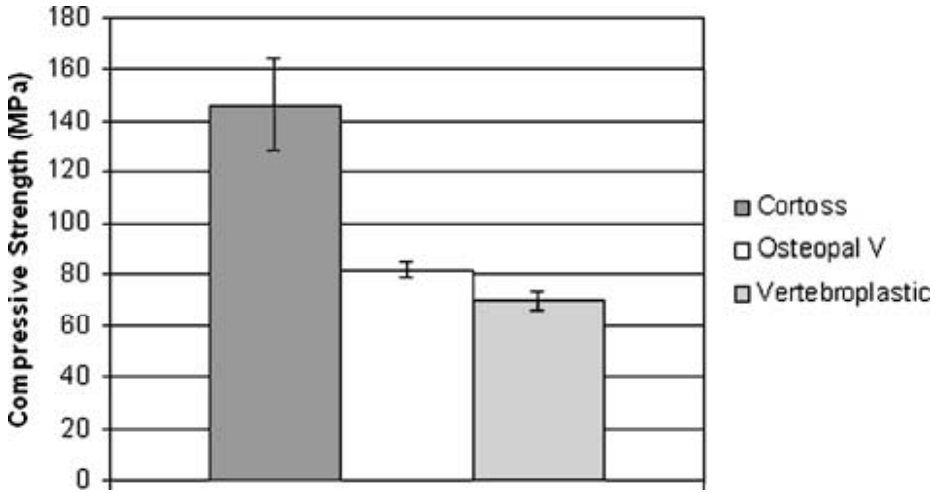
Cortoss

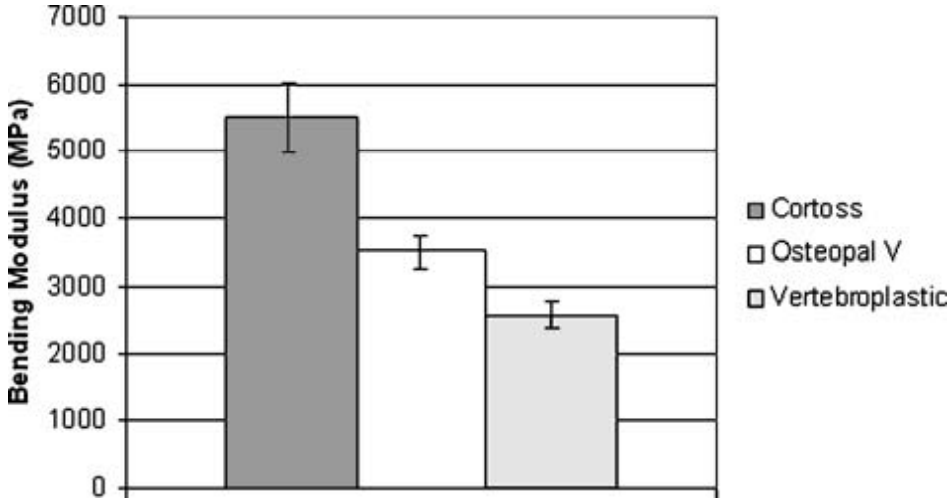


PMMA

1. A Prospective Randomized FDA-IDE Trial Comparing Cortoss With PMMA for Vertebroplasty SPINE Volume 37, Number 7, pp 544–550 (2012)

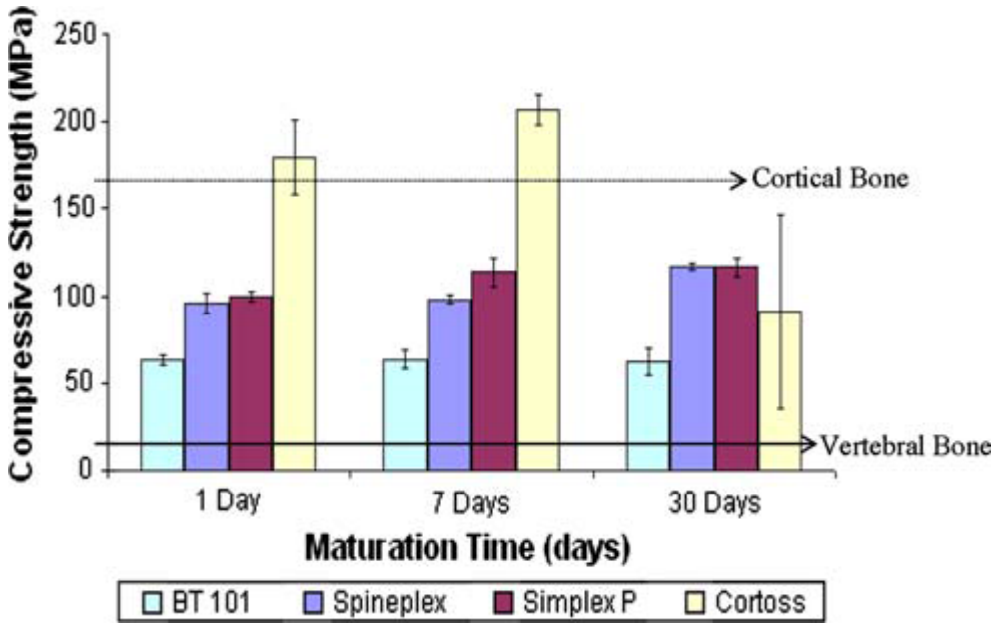
# Cortoss™ Mechanical Property Comparison




1. Sabina Gheduzzi · Jason J.C. Webb · Anthony W. Miles, J Mater Sci: Mater Med 17: 421–426 (2006)

# Cortoss™ Strength Loss with Time




1. D. Boyd , M. R. Towler , A. Wren , O. M. Clarkin J Mater Sci: Mater Med 19:1745–1752(2008)

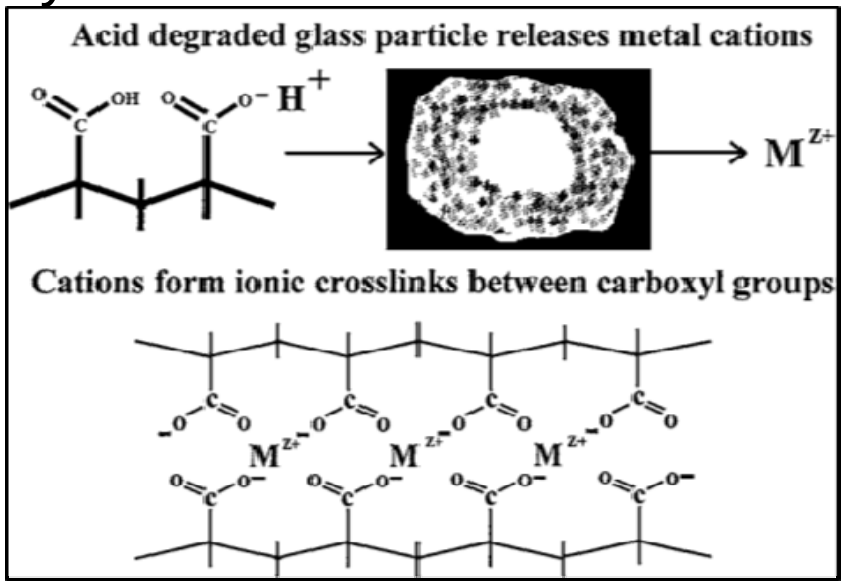
# Bioactive Resin VCF Composite- Cortoss™

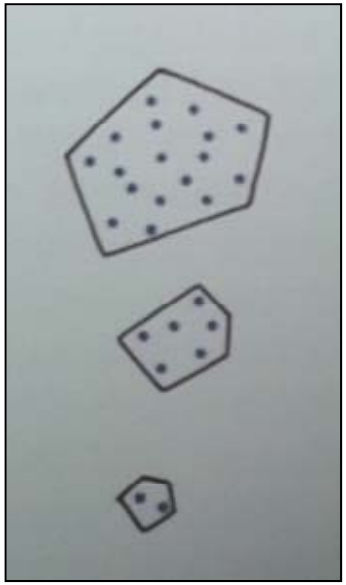
**Disadvantages**

- Exotherm- 63$^{0}$C
- bisEMA more prone to water uptake
  - Plasticisation of matrix – loss of stifness
  - Solubility of large Bioglass particles results in swelling and micro-cracking of matrix – loss of strength
- Bioactivity modest given majority of Bioglass is in crystallised form
- Relatively hydrophobic (though better than conventional PMMA cements) – bone wetting / apposition limited

# Glass Ionomer Cements

- Bioactive cement system
- Ion leachable glass powder, poly (acrylic) acid and water
- Carboxylic acid hydrolyses and degrades the glass, releasing ions
- Ions are chelated with $COO^-$ groups
- Crosslinking of the polyacrylate chains, embedding glass particles in polysalt matrix




4. De Barra, E. & Hill, R. 1998. Influence of poly(acrylic acid) content on the fracture behaviour of glass polyalkenoate cements. *Journal of Materials Science,* 33, 5487-5497.
5. Wilson, A. D. & McLean, J. W. 1988. *Glass-Ionomer Cement*, Quintessence Publishing Co.

# Ionomer Glasses

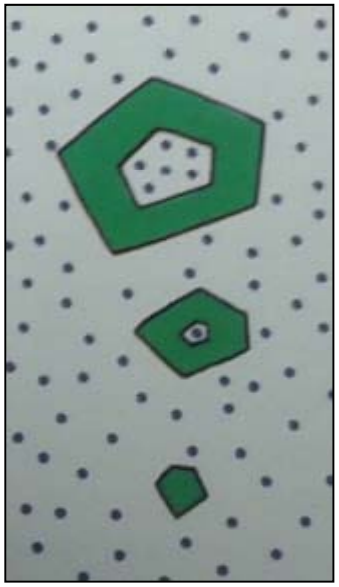
- Fluoro-alumino-silicate glass
- Glass is designed to contain a similar ratio of Ca–P cations for bone formation (If heat-treated crystallises to apatite and mullite)
- Therapeutic release of fluoride anions by cement reduces the risk of secondary caries (dentistry) and stimulates bone deposition (orthopaedics)

# Setting Reaction

- Gelation
  - Critical pH and ion concentration is reached
  - Soluble ions will precipitate to insoluble polyacrylates
  - Calcium polyacrylates responsible for the initial setting of the cement
  - Hardening of the cement due to the slower formation of aluminium polyacrylates
  - Chain entanglement, hydrogen bonding and weak ionic bonding also play a role in the gelation phase

# Setting Reaction

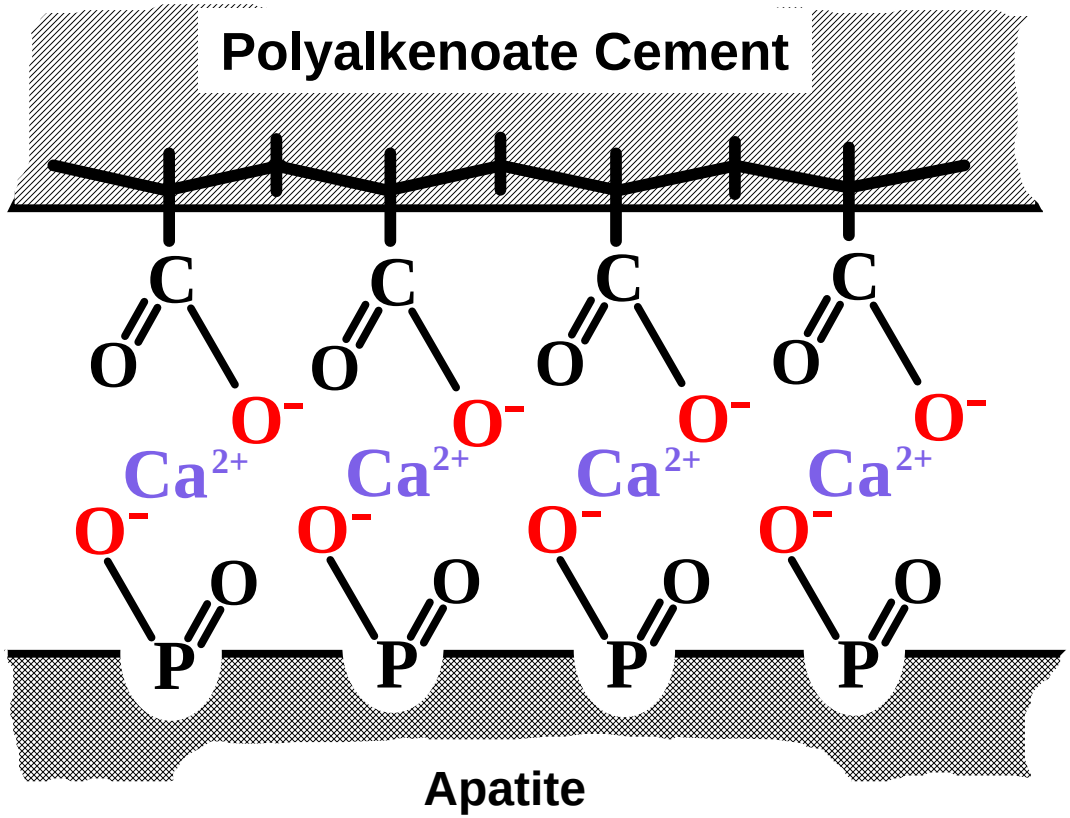
- Maturation
  - Hardening and precipitation process continue for up to 24hrs
  - Cements strength increase for up to a year, this is attributed to the ongoing conventional reaction
  - Results in an increase in the stability of the cement due to an increase in bound water
  - An increase in the crosslinking of the cement is thought to occur due to increasing aluminium ions relative to calcium ions in the matrix



# Properties of Glass Ionomer Cements

- Set at body temperature, without the liberation of heat.
- No appreciable shrinkage on setting
- Wet hydrophilic surfaces.
- Adhesive to bone and metallic devices
- Mild inflammatory response on placement as weak organic acid is quickly neutralised.

# Adhesion

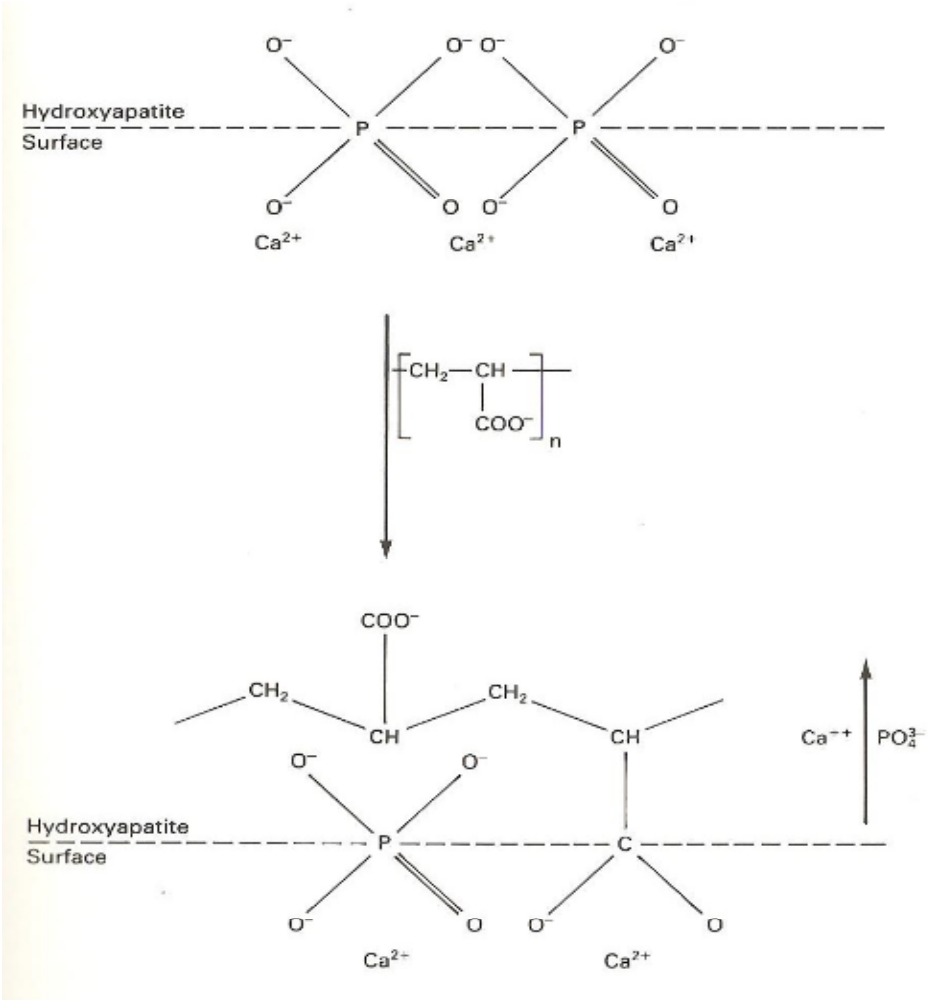


# Adhesion

- Chemically bond to dentin and bone
- Formation of chemical complexes to substrate i.e. dentine, enamel, cortical and cancellous bone
- Bond to both the organic (collagen) and inorganic (apatite) components
- Adheres to any coherent oxide/passivating layer ie $TiO_2$, $Cr_2O_3$, NiO

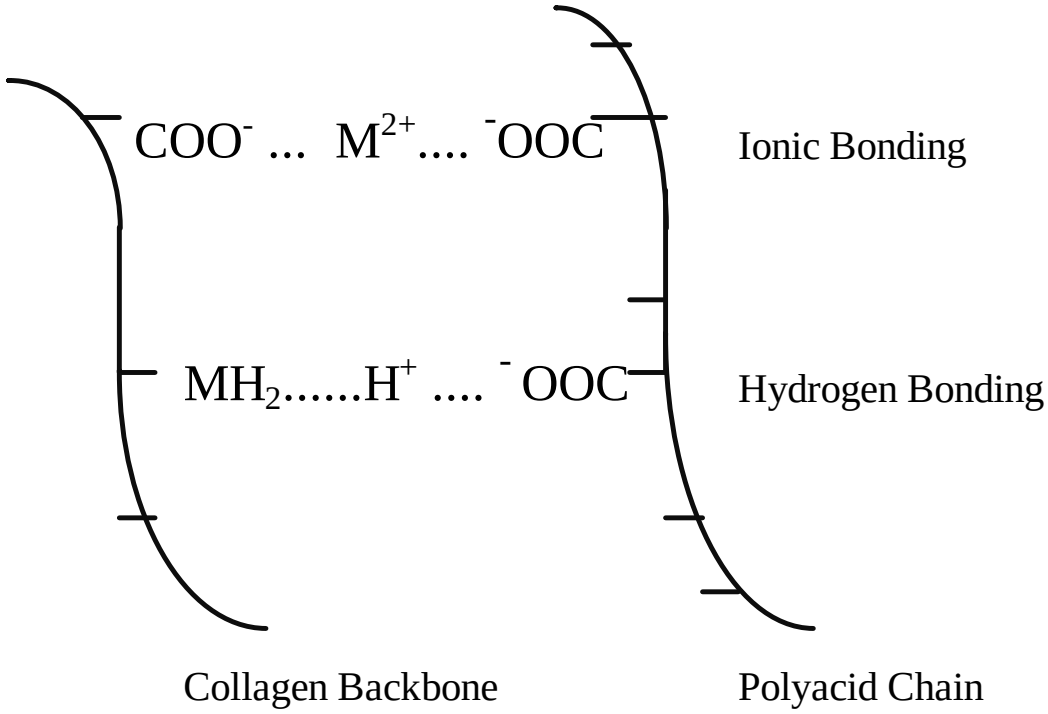
# Adhesion

# Adhesion




6. Wilson, A. D., Prosser, H. J. & Powis, D. M. 1983. Mechanism of Adhesion of Polyelectrolyte Cements to Hydroxyapatite. *Journal of Dental Research,* 62, 590-592.

# Adhesion


$COO^- \ldots M^{2+} \ldots {}^-OOC$
Ionic Bonding
$MH_2 \ldots\ldots H^+ \ldots {}^- OOC$
Hydrogen Bonding
Collagen Backbone
Polyacid Chain

# Comparison between GIC and PMMA Cements

| GIC | PMMA |
| --- | --- |
| • Chemically adhere to bone and dentin | • Mechanically adhere to bone |
| • No exotherms on setting | • Thermal necrosis of tissue due to large exotherms on setting |
| • No shrinkage of the cement | • Shrinkage due to polymerisation |
| • Therapeutic release of ions such as fluoride | • Chemical necrosis due to leaching of monomer |

# GPA cement applications:

(1) restorative tooth filling materials

(2) luting cements (adhesives)

(3) Otological devices

(4) Crannio/Maxillofacial reconstruction**

(5) Alveolar ridge enhancement

GPA cements have the potential to be used as bone substitutes and cements

# Deficiencies of Commercial GICs

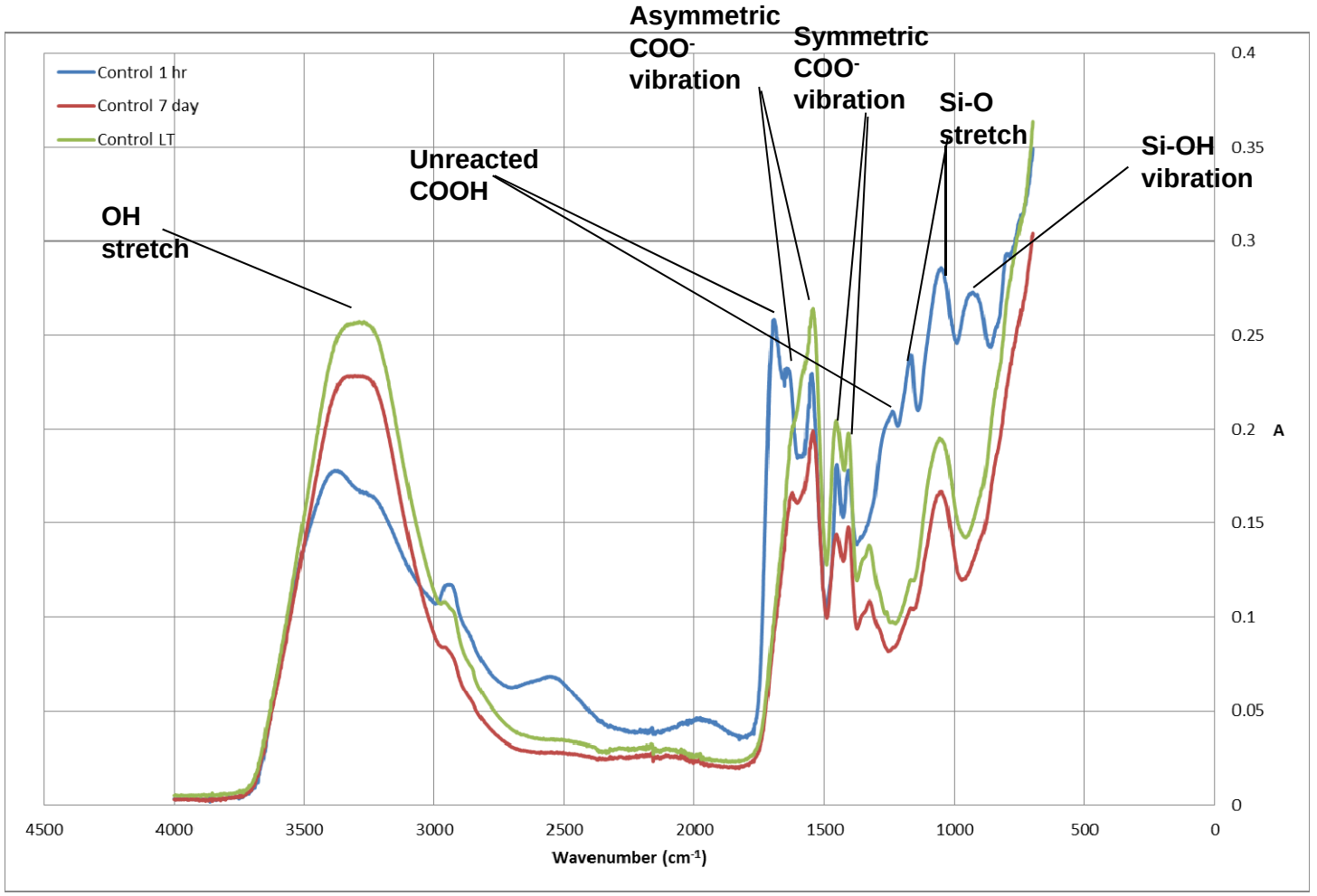
– Brittle material, lacks the toughness and fracture toughness for high load bearing applications

| | Bone | GIC Commercial |
|---|---|---|
| ***Modulus*** | 7 – 20 GPa | 8 – 10 GPa |
| ***Toughness*** | 1500 J/m$^2$ | 150 J/m$^2$ |
| ***Fracture Toughness*** | 0.5 – 2.2 MPa$\sqrt{m}$ | 0.7 – 0.9 MPa$\sqrt{m}$ |

# Factors effecting GIC mechanical properties

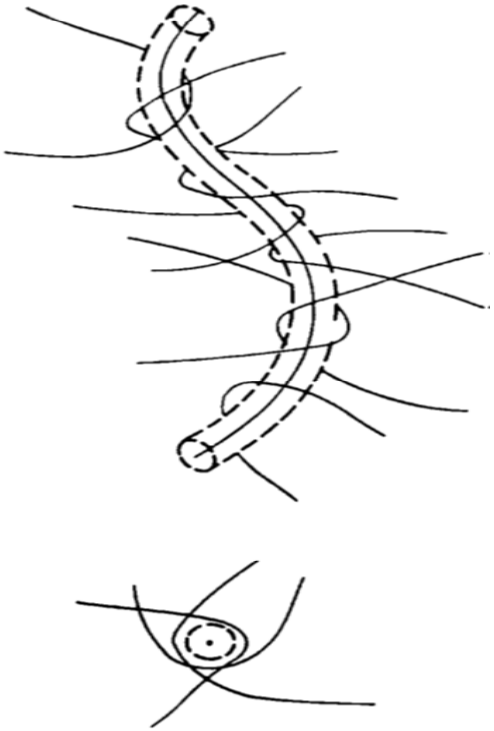
- Glass reactivity and composition
- PAA molecular weight
- Use of copolymers
- Particle size and morphology of powders
- Conditioning the glass particles

# FTIR


Asymmetric COO- vibration
Symmetric COO- vibration
Si-O stretch
Si-OH vibration
Unreacted COOH
OH stretch
Control 1 hr
Control 7 day
Control LT
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
A
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Wavenumber (cm-1)

# Fracture of GICs

- GICs exhibit thermoplastic polymer behaviour
- Reptation pull-out model by Prentice[8]
- Polymer chain trapped in a tube of entanglements formed by neighbouring chains
- $G \propto (M_n)^2$ this implies the slope should be 2



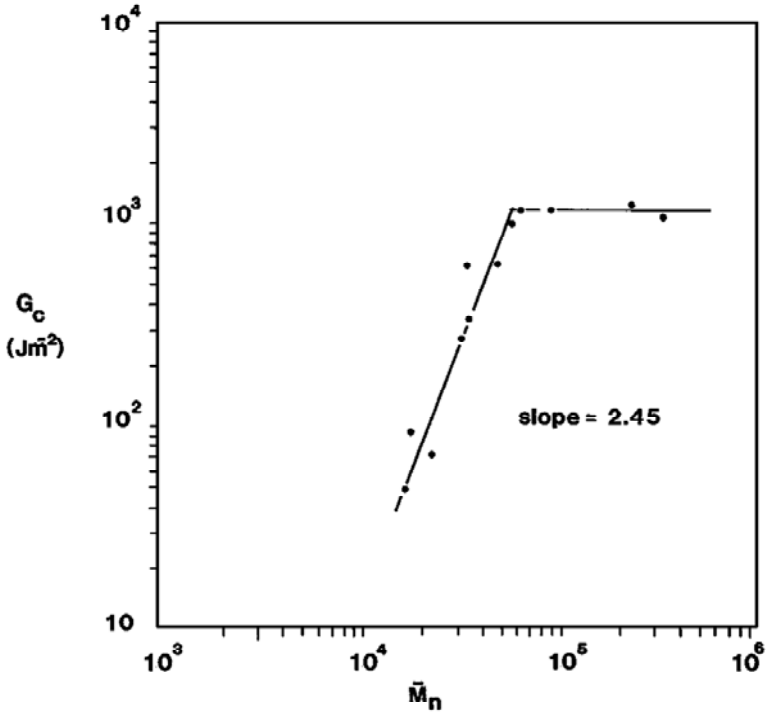


8. Prentice, P. 1985. The influence of molecular weight on the fracture of thermoplastic glassy polymers. *Journal of Materials Science*, 20, 1445-1454.

# Fracture of GICs

Assumptions

- Polymer crosses the fracture plane only once
- No distortion of the tube, distortion requires more work to remove the chain, increasing the plastic zone size
- Assumed that the polymer is monodisperse, whereas it has a polydisperse distribution

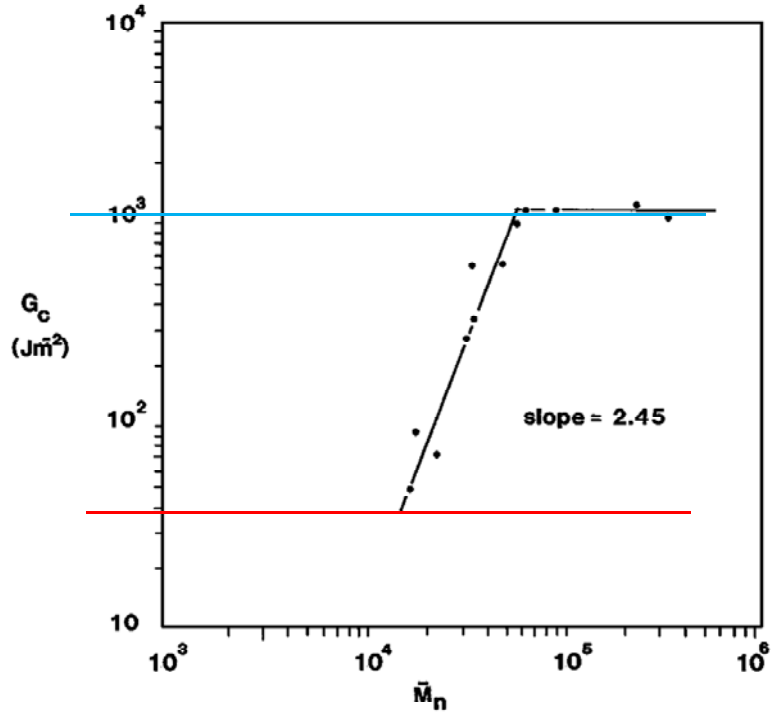





8. Prentice, P. 1985. The influence of molecular weight on the fracture of thermoplastic glassy polymers. *Journal of Materials Science*, 20, 1445-1454.

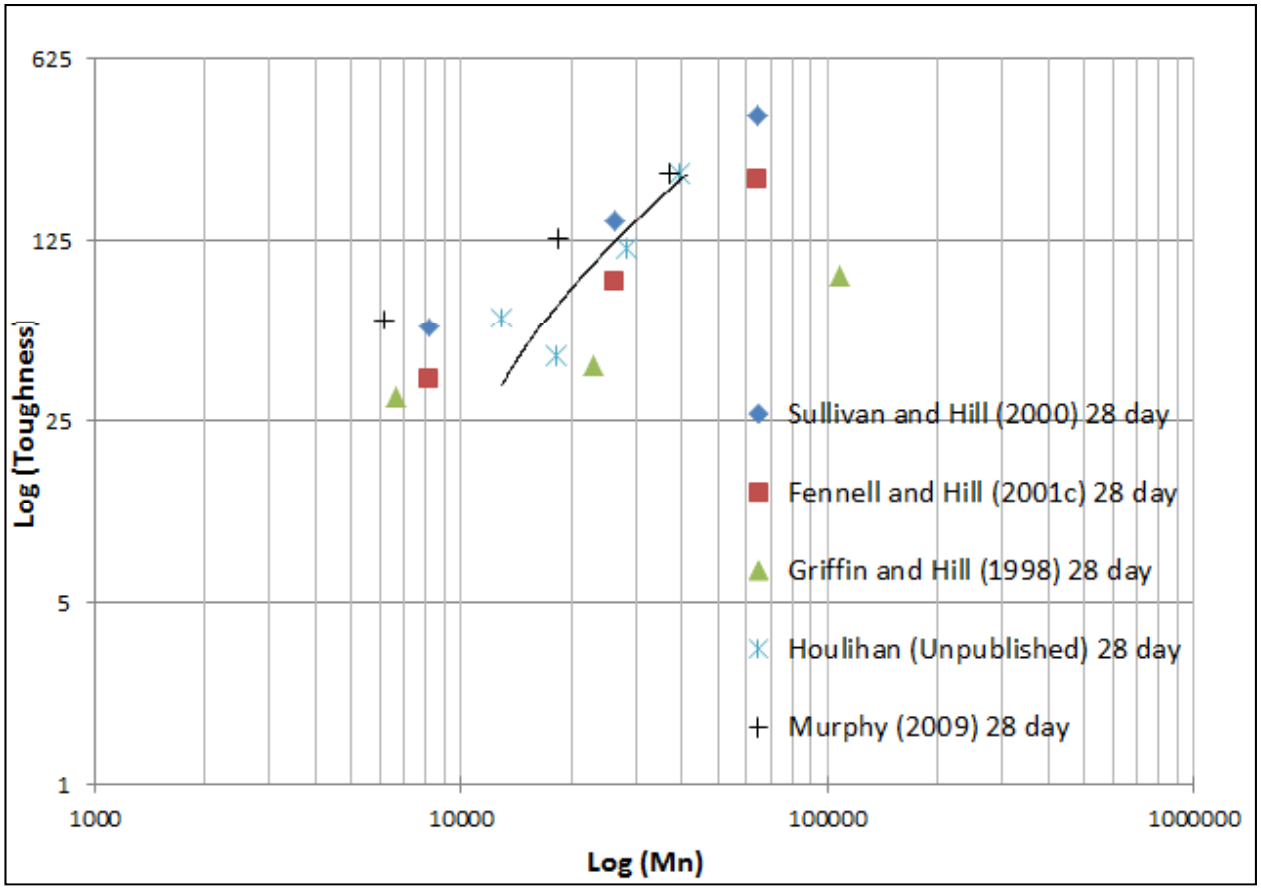
# Fracture of GICs

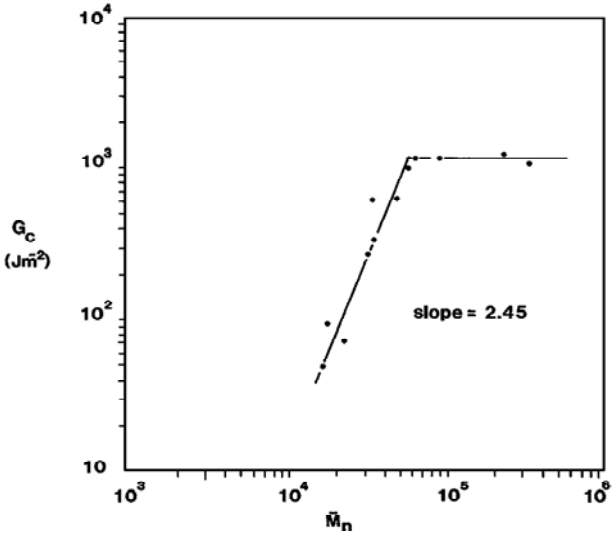
- Dependency of toughness on the $M_n$ of the polymer
- Once the critical molar mass is reached, the toughness is independent of $M_n$
- Force to remove the chain from its tube is greater than that to break the C-C bond of the polymer backbone



# Effect of $M_n$

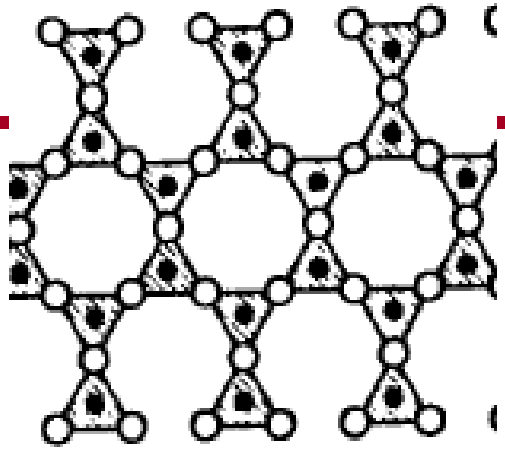
**Toughness (G)**



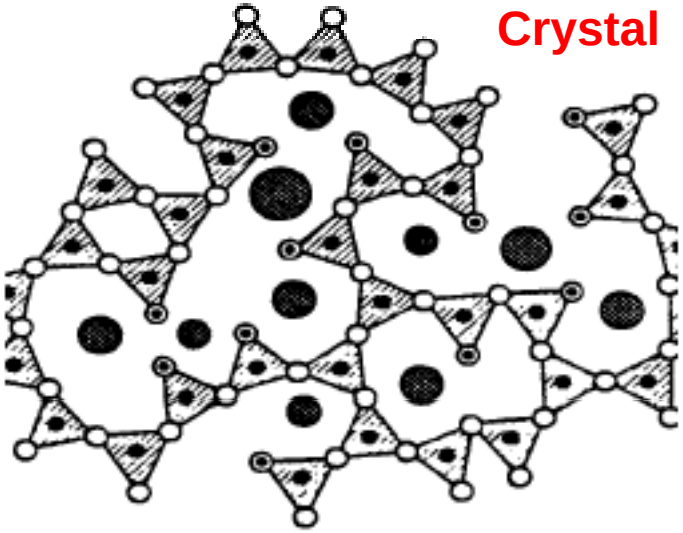



# Glass Structure

- Crystal - Fixed Bond Angles and Distances. Regular Periodic Structure. Low Energy State.



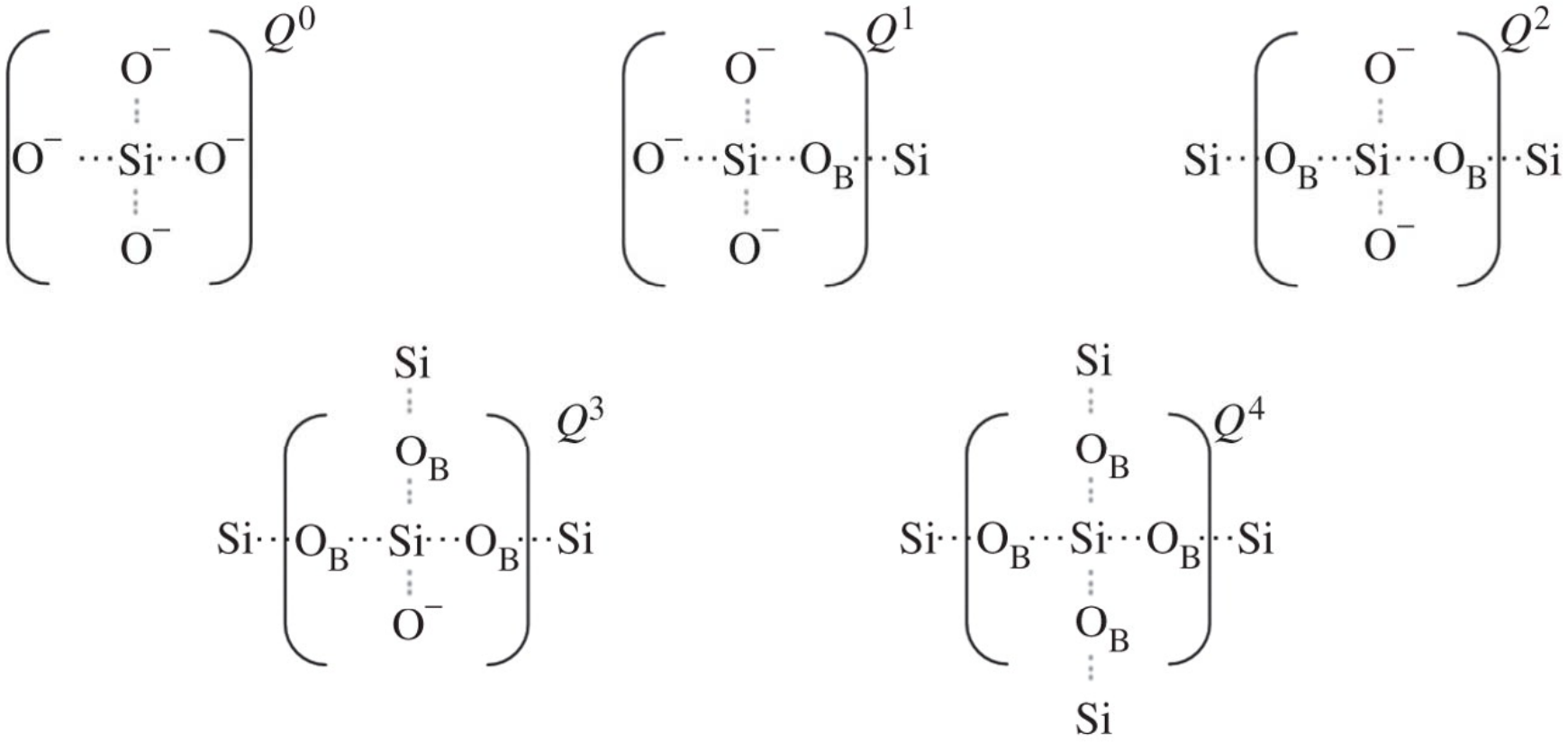
- Glass – Variation in Bond Angles and Distances. Disordered and High Energy State. Exhibits a Glass Transition.
- Produced by rapid quenching of a molten liquid.



# Glass Structure (2)

- **Glasses comprise:**
- Network Formers. Form the 3D backbone of the glass. Eg $SiO_2$.
- Network Modifying Oxides. Break up the glass network eg $Na_2O$, $K_2O$, CaO, SrO.
- Bridging Oxygens (Si-O-Si).
- Non-Bridging Oxygens $Si\text{-}O^-\ Na^+$.

# Schematic of the different Q structures that can describe Si network connectivity in glasses.




$O_B$ represents a network-forming bridging oxygen

# Network Connectivity

$$NC = 2 + \frac{[(2 \times SiO_2) + (2 \times P_2O_5)] - [2(M_2^IO + M^{II}O)]}{SiO_2 + (2 \times P_2O_5)}$$

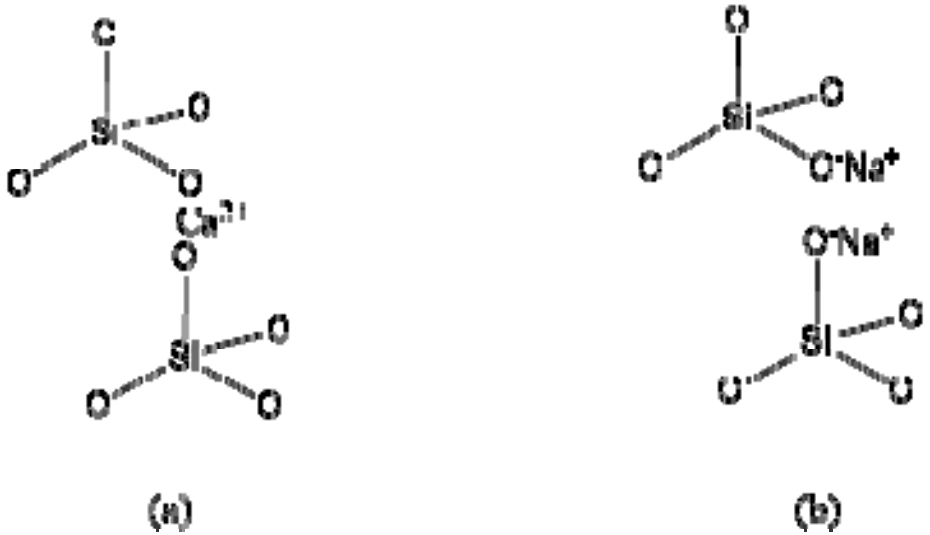
The formula above assumes that P atoms are in network forming role in a range of $Q^n$ structures, and the version below assumes that P is an orthophosphate $Q^0$ structure and requires modifier cations in a charge balancing role

$$NC = \frac{4[SiO_2] - 2[M_2^IO + M^{II}O] + 6[P_2O_5]}{[SiO_2]}$$

where $M_2^IO$ and $M_2^{II}O$ are the mono- and divalent modifier oxides in the glass

# Example Ionomer Glass -Sodium Series (1993!)

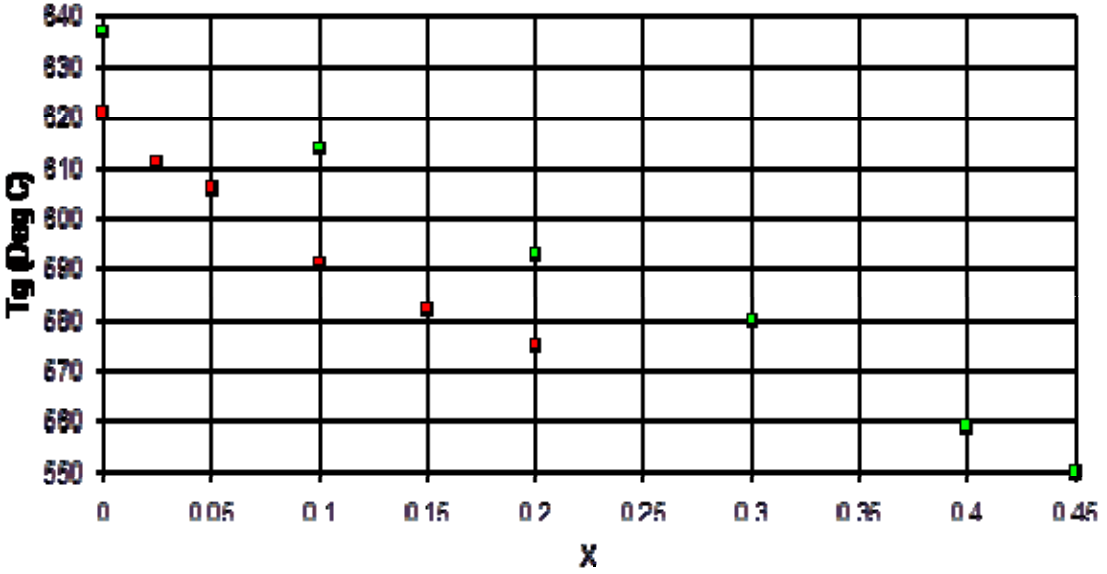
$1.5SiO_2$. $1.0Al_2O_3$ $0.5P_2O_5$. 1-X$CaO$.$0.5CaF_2$ X$Na_2O$
where X= 0.1, 0.2, 0.3 and 0.4.




Hypothesis: Replacement of structure on lhs by that on rhs would reduce Tg and increase reactivity. Many aspects of structure unknown at the time (role of F) – Properties difficult to interpret at the time

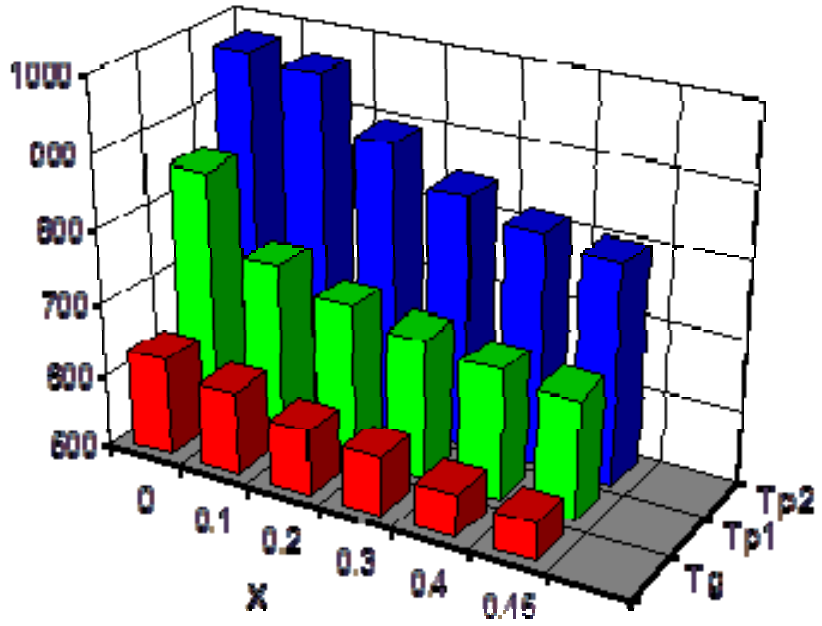
# Example Ionomer Glass -Sodium Series

$1.5SiO_2$. $1.0Al_2O_3$ $0.5P_2O_5$. 1-X$CaO.0.5CaF_2$ X$Na_2O$
where X= 0.1, 0.2, 0.3 and 0.4. Na = Green, K = Red



# Example Ionomer Glass -Sodium Series DSC

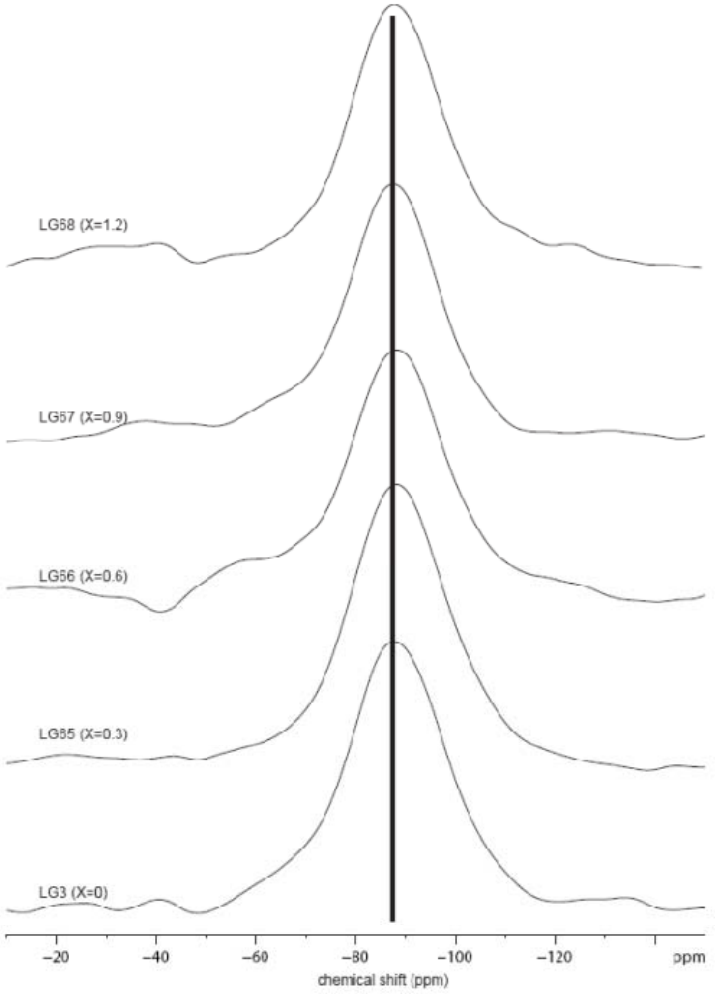
$1.5SiO_2$. $1.0Al_2O_3$ $0.5P_2O_5$. 1-X$CaO$.$0.5CaF_2$ X$Na_2O$




**Glass Transition Temperatures and First and Second Peak Crystallisation Temperatures For $1.5SiO_2.O.5P_2O_5.Al_2O_3.XR_2O.(1\text{-}X)CaO.0.5CaF_2$ Glasses**

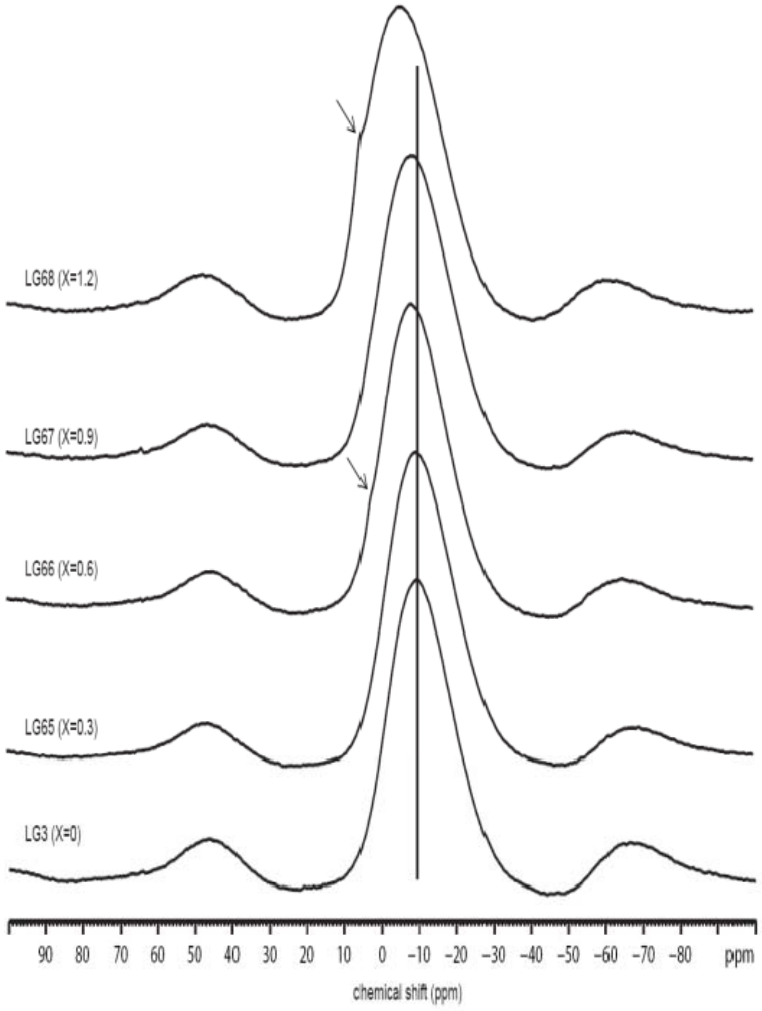
# Example Ionomer Glass -Sodium Series $^{29}$Si MAS-NMR

$^{29}$Si MAS-NMR spectra of sodium glasses
All glasses demonstrate the same chemical shift at around -87.0 to -88.0 ppm. Predominantly $Q^3$ structure, but unchanged by Na substitution



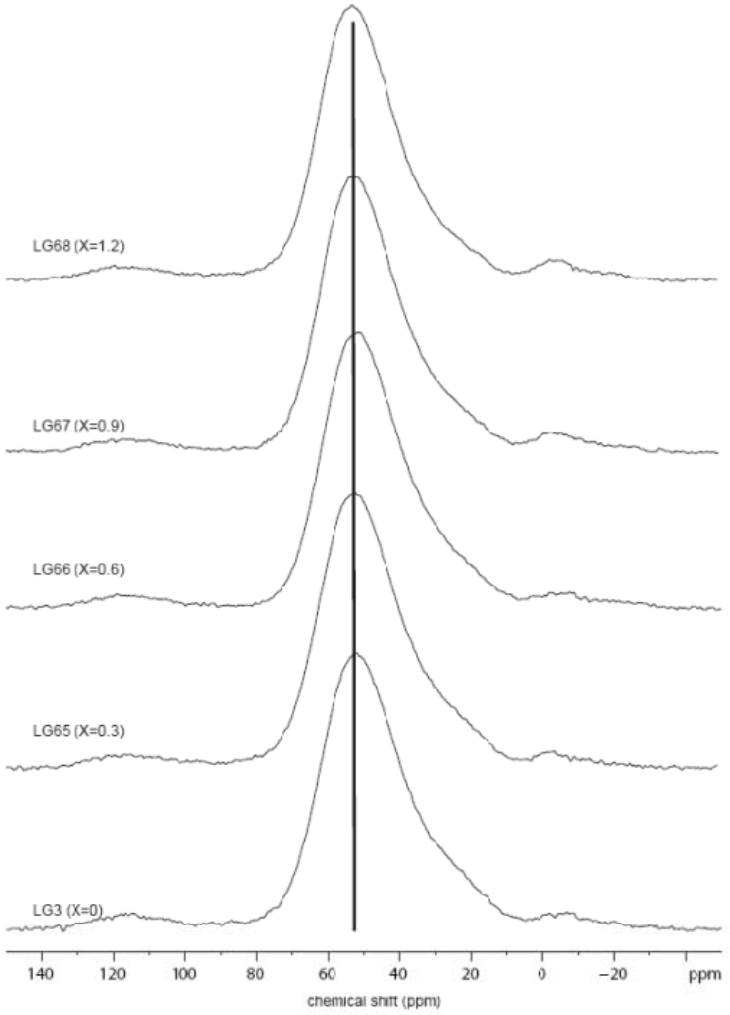
# Example Ionomer Glass -Sodium Series $^{31}$P MAS-NMR

$^{31}$P MAS-NMR spectra of sodium glasses of LG3, LG65, LG66, LG67 and LG68. Shows P is in $Q^1$ pyrophosphate role and with sodium increase shoulder appears (arrow) indicating some $Q^0$ orthophosphate formation



# Example Ionomer Glass -Sodium Series $^{27}$Al MAS-NMR

$^{27}$Al MAS-NMR spectra of sodium glasses The chemical shift remains the same for all the glasses. The major peak at around 52.0-53.0 ppm is Al(IV) and there is also a shoulder for Al(V) sites and a small peak at -2.0 ppm for Al(VI) sites. The line is a guide to the eye only

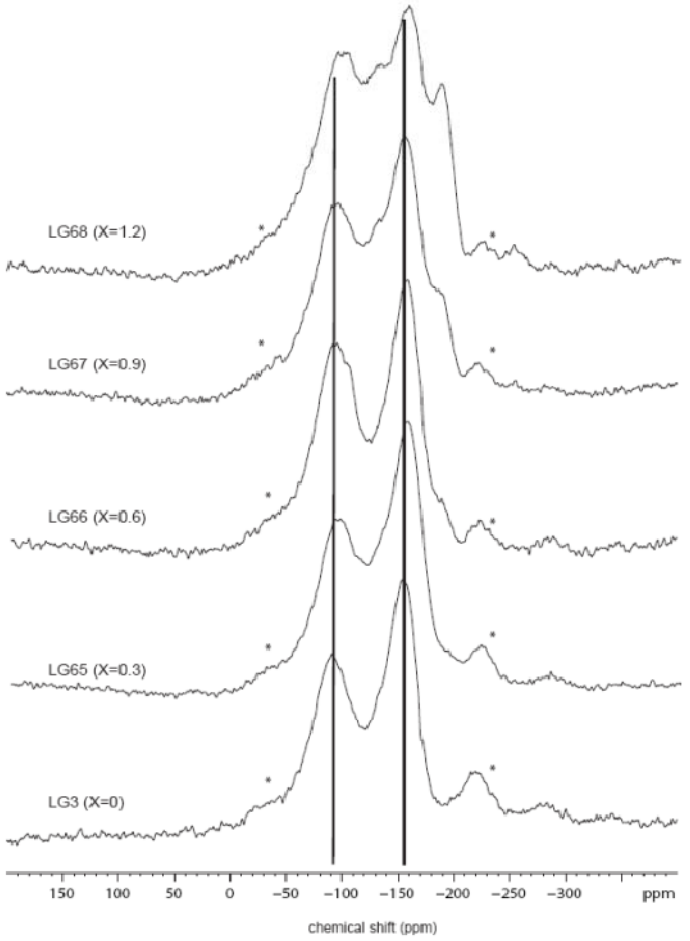


# Example Ionomer Glass -Sodium Series

$1.5SiO_2$. $1.0Al_2O_3$ $0.5P_2O_5$. 1-XCaO.$0.5CaF_2$ $XNa_2O$

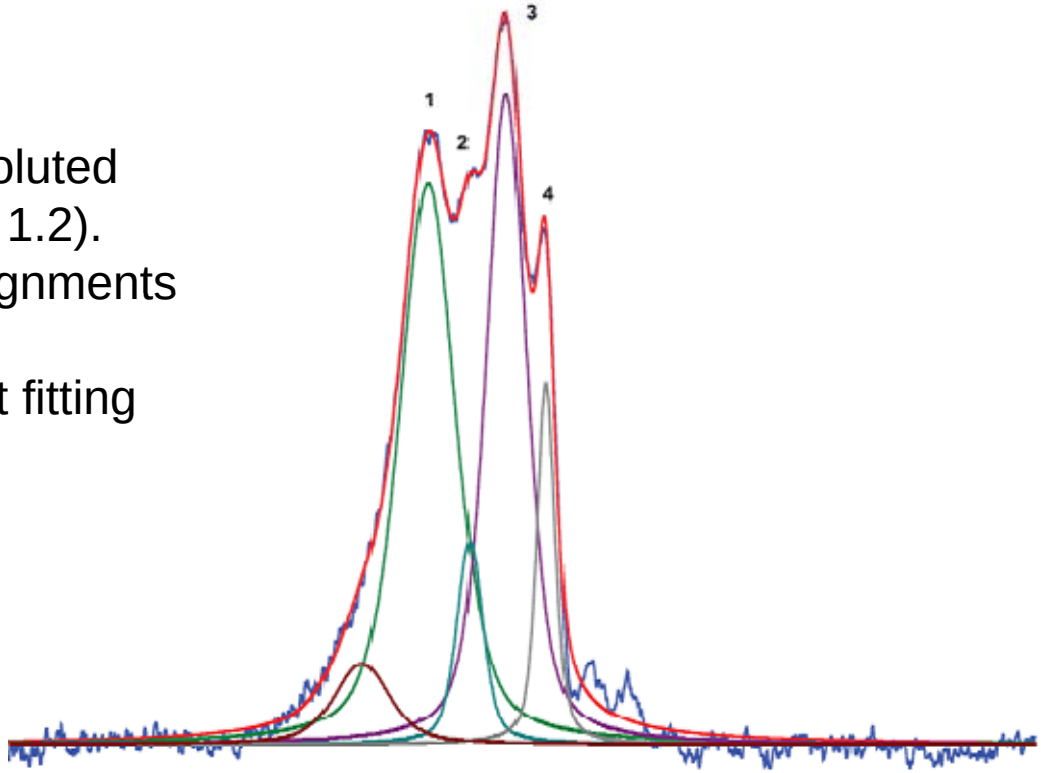
**19F MAS-NMR spectra of sodium glasses of LG3, LG65, LG66, LG67 and LG68**

There are two major peaks at -100.0 and -150.0 ppm corresponding to F-Ca(n) and Al-F-Ca(n). As the amount of sodium in the glass is increased, another two peaks appear at around -132.0 ppm which correspond to a mixed site of F-Ca/Na and at -186.0 ppm for Al-F-Na(n) site. The spinning sidebands are indicated by (*) and the lines are a guide to the eye only



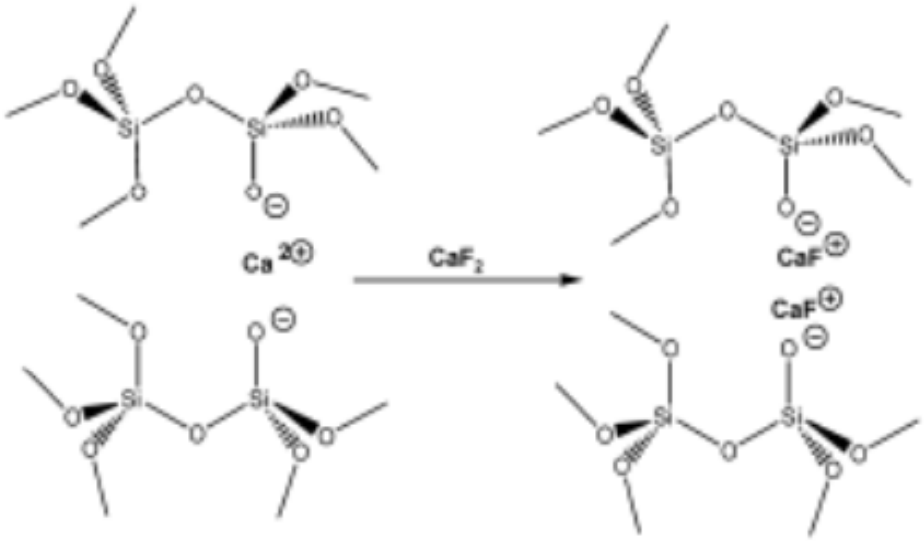
# Example Ionomer Glass -Sodium Series

The experimental and the de-convoluted spectra of the LG68 glass ($Na_2O$ = 1.2).
Peak labels correspond to the assignments given in Table
Fittings were performed using dmfit fitting program Gaussian model



# Example Ionomer Glass -Sodium Series

| Peak | Species | Chemical shift, ppm | Percentage |
|---|---|---|---|
| **1** | F-Ca(n) | -97.7 | **44.9** |
| **2** | F-Ca(3)Na(1) | -130.2 | **7.6** |
| **3** | Al-F-Ca(n) | -158.3 | **37.8** |
| **4** | **Al-F-Na(n)** | **-189.0** | **9.6** |



# Example Ionomer Glass -Sodium Series

Conclusion:

Presence of fluorine in these glasses can be present as

- fluorine calcium complexes
- mixed fluorine calcium complexes
- non bridging fluorines as aluminium fluorine complexes charge balanced by either calcium or sodium.

Substitution of Ca by Na changes the ratio and type of these speciations

# Structural roles in Ionomer and Bioactive Glasses

$SiO_2$
- increases network connectivity
- reduces bioactivity
- rate of network dissolution decreases

$P_2O_5$
- increases surface reactivity
- increases bioactivity
- increases degradation rate
- high conc's result in adverse effects

CaO, $Na_2O$
- reduce network connectivity

# Structural roles in Ionomer and Bioactive Glasses

F
- increase bone formation at low conc's
- toxic at high conc's

Mg, K, B
- little effect on bioactivity

Al
- increases network connectivity
- can inhibit bone bonding
- increases resistance to ion exchange surface reactions
- interferes with osteoblast and fibroblast metabolism

Ta, Ti, Sb, Zr
- increase network connectivity

# Predicting the bioactivity of glasses using the network connectivity or split network models

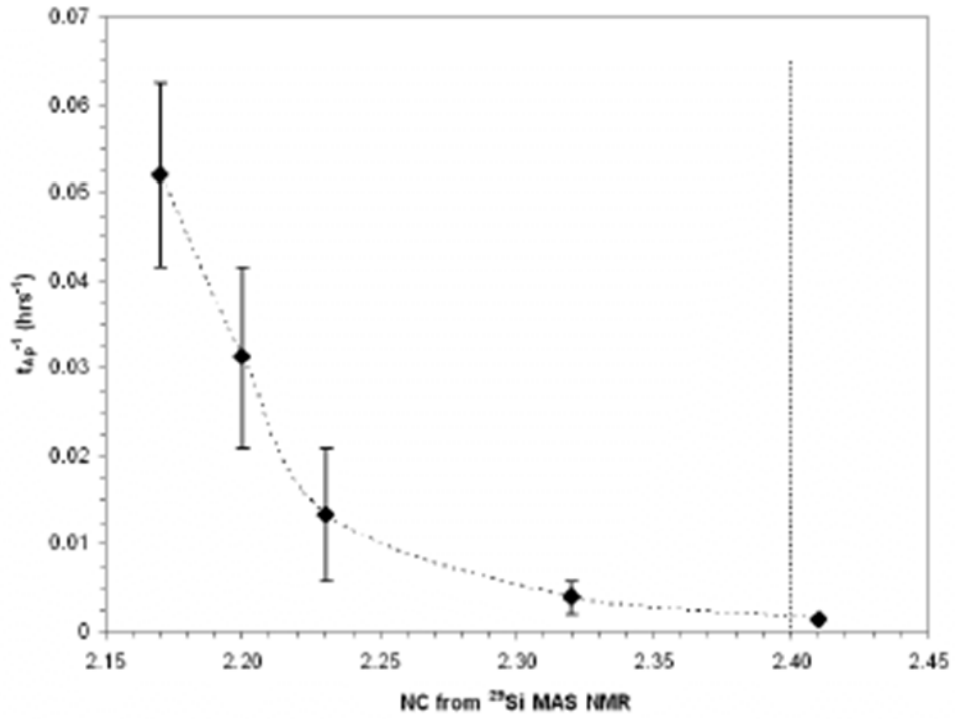



**Figure 1:** Bioactivity (defined as $t_{Ap}^{-1}$, where $t_{Ap}$ is the time of first apatite formation in SBF as detected by XRD) of BG in the Mg series *vs.* $NC_{NMR}$ calculated from the proportions of $Q^2$ and $Q^3$ silicons from $^{29}$Si MAS NMR [11]. The vertical line represents the percolation point (NC = 2.4), i.e. the cut-off value for bioactivity as defined by Hill [7].

Robert G. Hill, Delia S. Brauer Journal of Non-Crystalline Solids 357 (2011) 3884–3887

# Predicting the bioactivity of glasses using the network connectivity or split network models

Conclusion:

The network polymerisation ($Q^n$ structure) strongly influences glass dissolution and subsequent apatite formation, and the NC or split network models are useful and successful in predicting bioactivity

i) They do not take account of the nature of the network modifying cations, in particular their charge to size ratio and their influence on the glass network.
ii) They equate glass dissolution directly to bioactivity.

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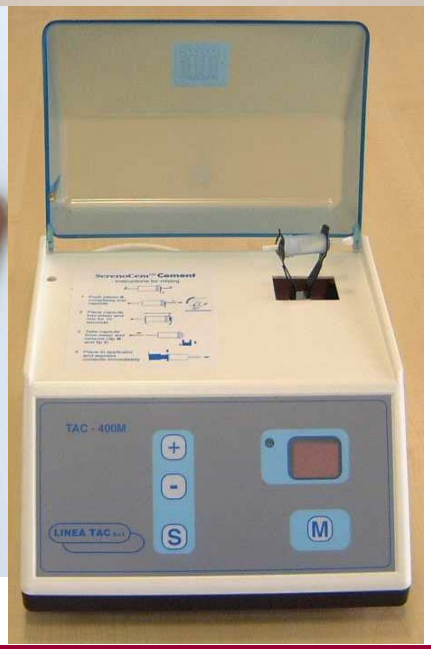
# Example Ionomer Glass –Fluoride Series

$$1.5SiO_2\ Al_2O_3\ 0.5P_2O_5\ CaO\ XCaF_2$$

| GLASS CODE | X |
|---|---|
| LG45 | 0.00 |
| LG44 | 0.25 |
| LG3 | 0.50 |
| LG26 | 0.66 |
| LG2 | 0.75 |
| LG42 | 1.00 |

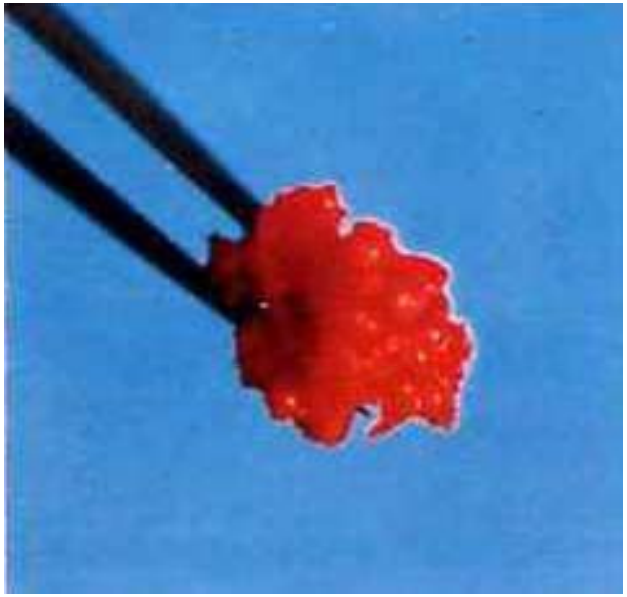
# Serenocem™ Capsules

$1.5SiO_2\ Al_2O_3\ 0.5P_2O_5\ CaO\ XCaF_2$



# Serenocem™ Granules


EM scan of granules, showing micro pores. magnification x 20



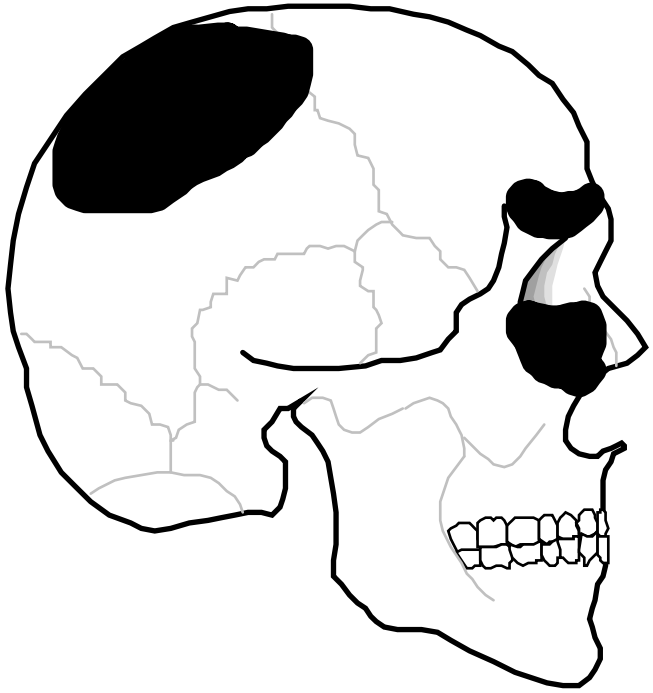
Hydrophilic granules absorb blood to produce fibrin clot.

Produced by incorporating $CaCO_3$ into the cement which generates $CO_2$ in-situ, foaming the cement . Sold as a cancellous bone substitute.

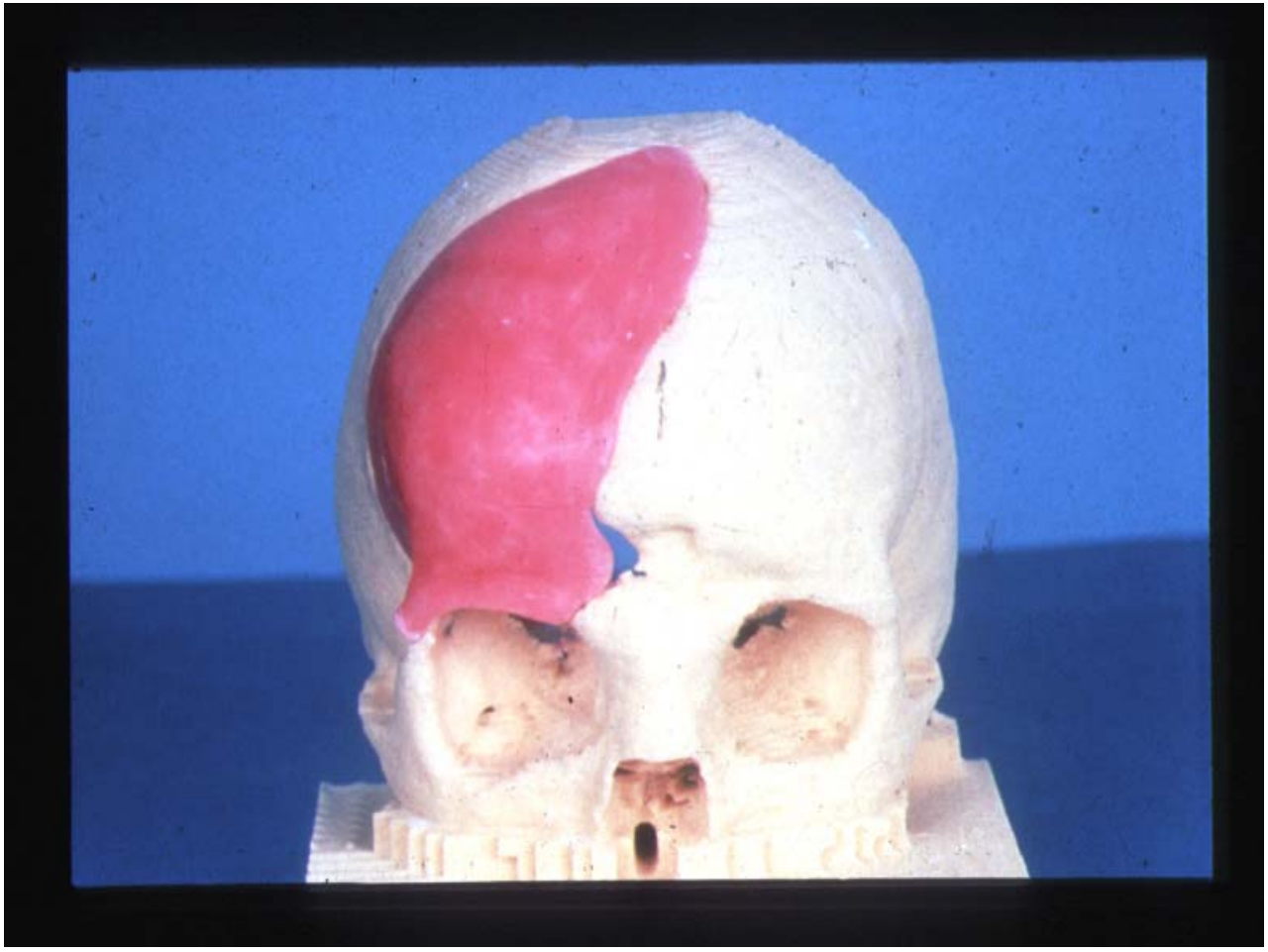
# GPA Cement BONE SUBSTITUTES

e.g. (a) Cranial bone plates

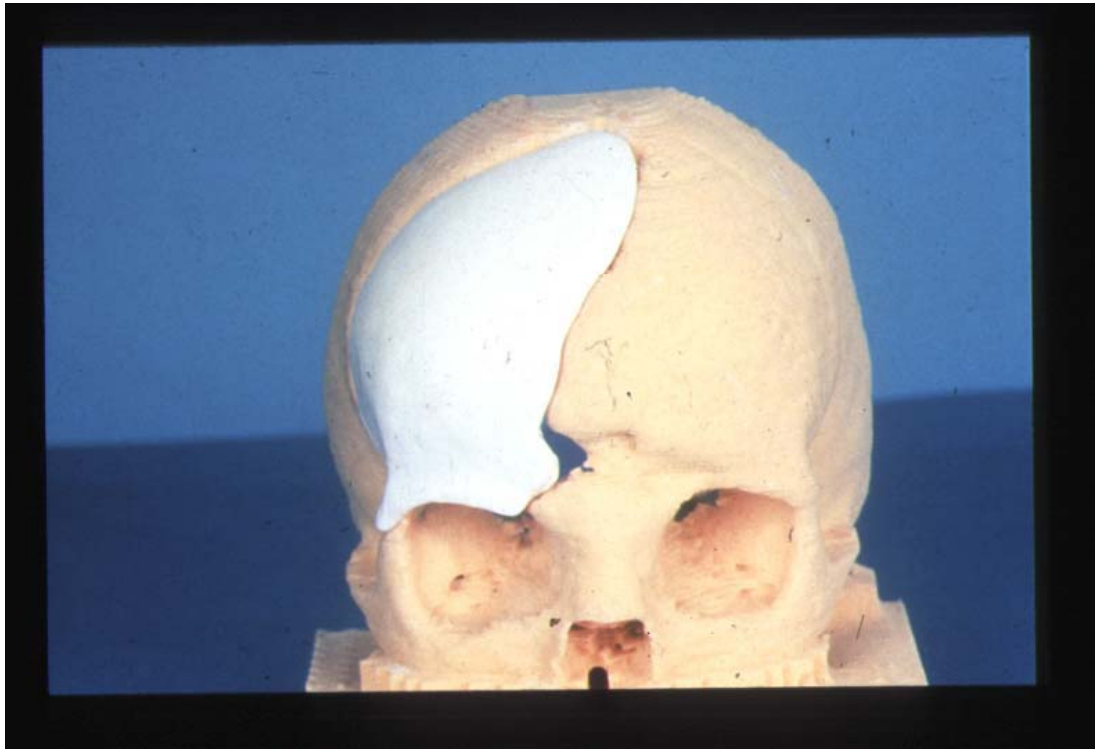
(b) Maxillofacial implants



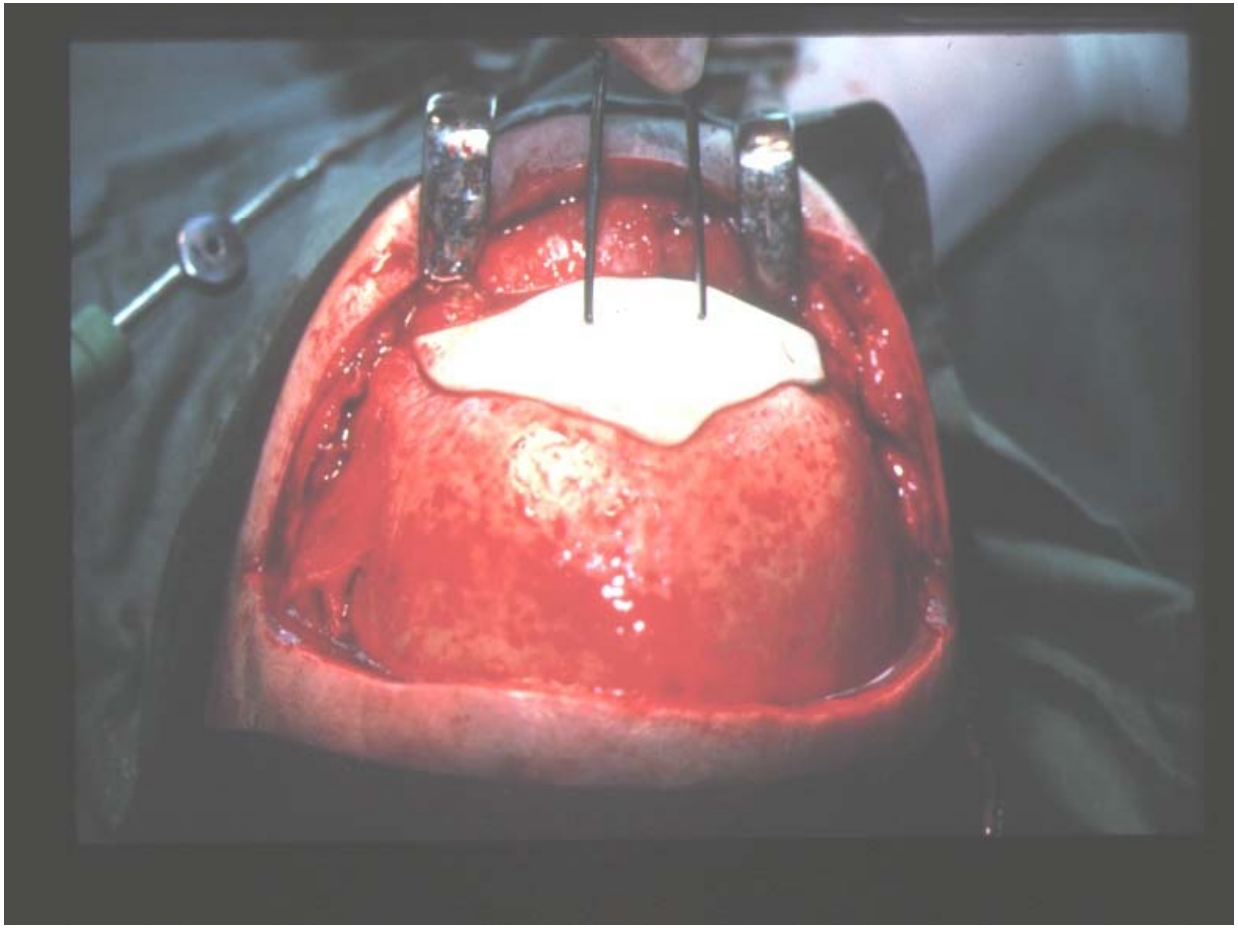
# Wax Impression formed via CAT Scan



# Custom Plate formed + Autoclaved



# Placement of GI Cranial Plate



NB This product off market

# Glass Ionomer cements

- Advantages
    - Non-exothermic setting reaction
    - Adhesive bond formed with bone and metals
    - Bioactive ions incorporated
    - Low systemic toxicity
    - Reduced local toxicity
- Disadvantages
    - Inferior mechanical properties
    - Neurotoxicity of Aluminium and PAA

# Acknowledgements

SS- NMR

- Prof Robert Hill QMUL
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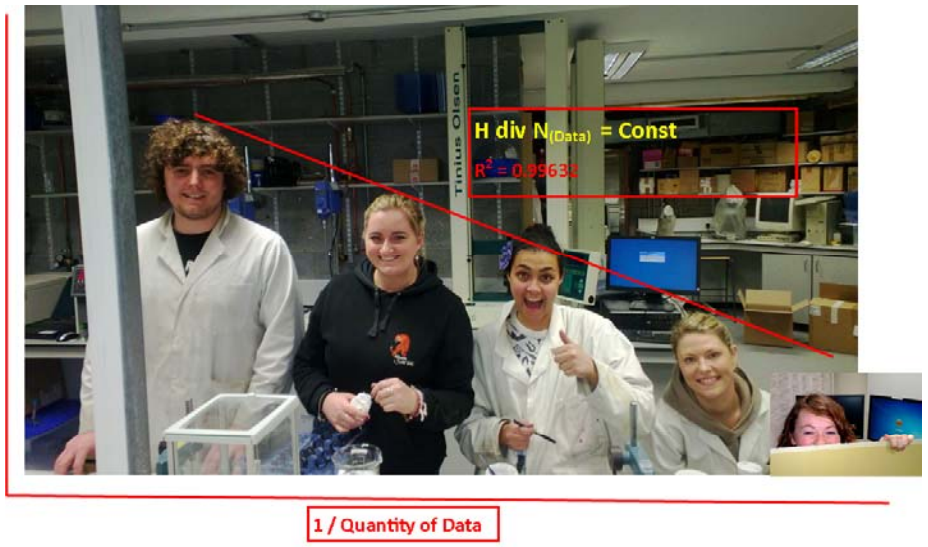
- Dr Rob V. Law Imperial

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