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Acknowledgements

This research was supported by the Ministry of Education, Czech Republic, Grant No. MSM 153100008.

Method for implementing bioluminescence-based analytical assays in nanolitre volumes

D. A. Bartholomeusz, R. H. Davis and J. D. Andrade
Department of Bioengineering, University of Utah, Salt Lake City, UT 84107, USA

Bioluminescence-based analytical assays in a miniaturized and stable format, can measure various analytes in nanolitre sample volumes. Nanoliter volumes of multiple bioluminescent analytical assays were deposited in an array format and lyophilized. ATP–firefly luciferase and NADH–bacterial luciferase platform reactions are compared. We achieved parallel sample delivery via sample-hydrated gels. The luminescence was measured by CCD and photodiode arrays. These miniaturized assays and instruments can be prepared as micro-analytical systems to operate in point-of-care (POC) diagnostic devices.

Multi-parametric experimental design of bioluminescence-based analytical assays

Y. Al-Sheikh,[2] J. Abernathy,[1] D. A. Bartholomeusz,[1] R. H. Davis[1] and J. D. Andrade[1]
[1]Department of Bioengineering, University of Utah, Salt Lake City, UT 84107, USA
[2]Department of Physics, University of Utah, Salt Lake City, UT 84107, USA

Multiparametric data analysis of bioluminescence-based analytical assays, lyophilized in the nL volume range, offers an inexpensive and efficient assay optimization method. Moreover, the various parameters associated with single or multiple bioluminescence-based analytical assays can be analysed in parallel. Optimization parameters include concentrations of enzymes and reagents, pH, on-board calibrations and references, interference effects, and error analysis. Efficient algorithms for multiparametric experimental design that can be used in these optimizations are presented. These algorithms will accelerate the development of new bioluminescence-based analytical assays for specific diagnostic panels as well as enhancing analytical accuracy and precision.

The first deep-sea observations of natural benthic bioluminescence using an *in situ* ISIT camera

E. J. V. Battle, P. M. Bagley and I. G. Priede
Oceanlab, University of Aberdeen, Newburgh, Aberdeenshire AB41 6AA, UK

An ISIT (intensified silicon intensifying target) camera mounted on an autonomous lander was used to observe bioluminescence produced by organisms on the sea floor of the Porcupine Seabight and Abyssal Plains regions of the north-eastern Atlantic ocean. The camera recorded natural bioluminescence (that occurring without human stimulation) without the need for lights, for up to 3 h after lander touchdown. Eighteen deployments carried out over 3 years, at depths of 970–4000 m, detected natural bioluminescence of organisms living on or near the sea floor. At most sites, 0.7 events/min were observed. However, one location at a depth of 1000 m on the Porcupine Seabight exhibited much higher levels of bioluminescence (on average, more than three bioluminescent events/min) in both spring and autumn. A control experiment without bait at this site elicited little bioluminescence. Large numbers of the cut-throat eel *Synaphobranchus kaupi*, some sharks and amphipods were observed at the bait. The source of the bioluminescence remains enigmatic, since these species of fish are not known to emit light. A dominant form of light emission appeared to be extrusion of luminescent material from the seafloor, suggesting a benthic infaunal source. This 'bioluminescent garden' is located close to known cold water coral mounds, which are sites of high biodiversity and hence may harbour bioluminescent fauna in greater abundance than elsewhere on the sea floor.

Bioluminescence variability of *lux*-marked strain *Escherichia coli* Z905/pPHL7 in aquatic microcosms with different salinity

A. N. Boyandin,[1] T. V. Kargatova,[2] E. E. Ganusova,[1] T. I. Lobova[2] and L. Yu. Popova[1]
[1]Institute of Biophysics, Siberian Branch of the Russian Academy of Sciences, Akademgorodok, Krasnoyarsk 660036, Russia
[2]Institute of Computational Modelling, Siberian Branch of the Russian Academy of Sciences, Akademgorodok, Krasnoyarsk 660036, Russia

The population dynamics and expression variability of the transgenic microorganism (TM) *Escherichia coli* Z905/pPHL7 (Ap^{r}Lux$^+$) bioluminescence genes cloned in a recombinant plasmid have been studied in artificial aquatic ecosystems with different salinity and bacterial species composition. It was shown that, in competition with indigenous microflora, the TM population was 2–4 times lower than in sterile freshwater and brackish microcosms.

Higher salt concentration in the medium led to differences in displaying the plasmid genes expression as compared to freshwater microcosms, independent of their complexity. Particularly, in brackish medium the bioluminescence expression reduced to a greater extent and was revealed only at plating into TM accumulative cultures with high content of selective factor (50–200 μg/ml ampicillin). TM clones isolated from freshwater microcosms maintained a higher bioluminescence level; at that for sterile microcosms it was higher than for non-sterile. Many clones could be seen during the plating of microcosm water samples on the selective media.

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OPTICAL FLUORO-IMMUNOSENSORS BASED ON PHOTO-AFFINITY LABELING TECHNIQUES

I-Nan Chang, Jinn-Nan Lin, James N. Herron and Joseph D. Andrade
Departments of Materials Science and Engineering and Bioengineering, University of Utah, Salt Lake City, UT 84112

The majority of current immunosensor designs are based on competitive immunoassays, which require fluorescent-labeled analytes as competing agents. Our approach is to employ a homogeneous immunoassay (no washing step required to separate free and bound analytes) based on a photo-affinity labeling technique. This technique is a general chemical strategy whereby antibody binding sites are selectively derivatized with fluorescent reporter molecules through a photoactive group. We suggest that when antigen binds to the fluorescent-labeled antibody, the microenvironment change, caused by the presence of the bound antigen, results in spectroscopic changes of the fluorophore. The goat anti-biotin polyclonal antibody was selected as model system and different dyes were chosen for testing this hypothesis. We expect that the changes of the fluorescence spectra of fluorophores will be related to characteristics of the fluorophores, including hydrophobicity, charges, and spacers.

Acknowledgement: This work was supported by Center for Biopolymers at Interfaces, University of Utah.

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SURFACE CHARACTERISTICS AND BLOOD COMPATIBILITY OF POLYSULFOALKYL METHACRYLATES

W.Y. Chen, J.D. Andrade, T. Okano, L. Dost and S.W. Kim

Department of Bioengineering, University of Utah
Salt Lake City, Utah 84112

In recent years heparinoid polymers have been synthesized and their anticoagulant activities evaluated and studied. We here report the surface characteristics in relation to the blood compatibility of polysulfoalkyl methacrylates.

Sulfoalkyl methacrylates(sulfoethyl methacrylate SSEMA, sulfohexyl methacrylate SSHMA, sulfooctyl methacrylate SSOMA and sulfodecyl methacrylate SSDMA) were copolymerized with hydroxyethyl methacrylate (HEMA) and methylene bis-acrylamide (MBAAM) as crosslinking agent. Prepolymers in water or dimethyl sulfoxide solutions were obtained after polymerizing at 60°C under nitrogen for 0.5-1.5 hours with ammonium persulfate as initiator. Glass slides, glass coverslips, or glass chips were coated with the prepolymer solutions followed by further polymerization at 65°C under vacuum and nitrogen for at least 16 hours.

Contact angle hysteresis measurement by the Wilhelmy plate method were listed in Table 1, which shows that the contact angle hysteresis increases and the receding angle decreases with increasing side chain length.

Table 1: Contact Angle Data

Samples	Contact Angles After Hydration for 3 h			24 h		
90 : 10 : 5 (mol)	θ_a	θ_r	$\Delta\theta$	θ_a	θ_r	$\Delta\theta$
polyHEMA-SSHMA-MBAAM	70.9	41.3	28.7	56.1	26.4	29.8
polyHEMA-SSOMA-MBAAM	74.0	34.5	39.5	59.7	22.7	37.0
polyHEMA-SSDMA-MBAAM	74.2	27.2	47.0	61.9	17.0	44.9

X-ray photoelectron analysis of the surface composition of these copolymers revealed a striking enrichment of the sulfonate groups on the surface, as shown in Table 2.

Table 2. Surface Composition of SSRMA Copolymers

Samples 90: 10 : 1 (mol)	Elemental Ratio C	O	S	Na
poly HEMA-SSDMA-MBAAM, cald	100.0	46.9	1.5	1.5
found	100.0	43.0	8.8	12.0
poly HEMA-SSHMA-MBAAM, cald	100.0	49.8	1.6	1.6
found	100.0	50.0	12.0	19.0
poly HEMA-SSEMA-MBAAM, cald	100.0	53.2	1.7	1.7
found	100.0	57.0	8.4	8.7

The amount of the charged groups were about 6-8 times in excess as compared with the theoretical values. The excess may be even greater in aqueous medium. This fact partly explains the significant change in blood compatibility of these copolymers as compared with polyHEMA.

Results of APTT tests of glass beads coated with polyHEMA and several samples of SSRMA copolymers by fibrometer showed very little difference. The WBCT test (dog blood) data are given in Table 3. The inner wall of test tubes were coated with polymer samples as above.

Table 3. WBCT of SSRMA Copolymers

Samples	Time (min.)
bare glass	10
poly HEMA	17.5
poly HEMA-SSHMA-MBAAM	22.5
poly HEMA-SSOMA-MBAAM	25.5
poly HEMA-SSDMA-MBAAM	29.5
poly HEMA-SSHMA	> 2 hr.
poly HEMA-SSOMA	> 2 hr.
poly HEMA-SSDMA	> 2 hr.

The molar ratio of HEMA to SSRMA in all these polymers was 9:1. Results of recalcification time tests were the same as those in the previous literature (1).

The in vivo blood compatibility of polyHEMA-SSOMA-MBAAM was investigated by coating the inside of polyester urethane tubes (i.d. 1.5 mm) with 1% solution and applying these tubes as A-V shunts in both jugular vein and carotid artery of adult New Zealand white rabbits (5-7 lbs.) for 5 hrs. Results from 3 experiments showed that the polymer had no influence on APTT, and the depletion of number (< 30%) and aggregability (40%) of rabbit platelets were acceptable.

The above results suggest that the anionic sulfoalkyl methacrylate polymers did not affect the intrinsic coagulation system but did show interaction with Ca^{++} ion and chiefly blocked the conversion of fibrinogen to fibrin.

In light of these results a set of preliminary static inhibition test of calcification was performed. Biomer film samples were coated with polyHEMA and polyHEMA-SSHMA-MBAAM, respectively, immersed in calcium barital buffer (calcifying solution), and incubated at 37°C with continuous shaking. The solution was changed daily for three days. Then the samples were removed, rinsed with distilled water, and extracted with EDTA decalcification solution for 24 hrs. The calcium concentration in the extracts were measured by atomic absorption photometry and expressed as $\mu g/cm^2$ surface area (average values of 4 samples) as listed in Table 4.

Table 4 Amount of Ca^{++} Deposited on the Polymer Surface

Samples	Ca^{++}, $\mu g/cm^2$	pH
poly HEMA	17.3	7.56
poly HEMA-SSHMA-MBAAM	0.6	7.56
poly HEMA-MAA (1%)	2.32	7.44
poly HEMA-MAA (3%)	13.5	7.44
Biomer	0.72	7.44

Comparing with the data obtained previously at pH 7.44 for poly HEMA-MAA etc., the results seemed promising, although the reason is not clear yet. It deserves further investigations.

1. W.Y. Chen, B.Z. Zu and X.D. Feng, J. Polym. Sci.: Polym. Chem. Ed., Vol. 20, 547-554 (1982).

CMOS Luminescence Detection Lab-on-Chip: Modeling, Design, and Characterization

Bioluminescence whereby light is emitted as a result of a chemical reaction offers several advantages over other photo-emissive detection methods such as fluorescence, including low background and the utilization of reagents with extended shelf life. Also, since no filters or excitation sources are needed, lab-on-chip integration is considerably easier. Commercial luminescence detection systems today use expensive cooled CCD-based camera setups and require large micro liter volumes of costly reagents due to the high loss in their optical paths.

There is growing need for miniaturized low cost biosensor systems for environmental and biomedical diagnostics. To address this need we have been investigating systems in which the luminescent chemistry is directly coupled to the detector surface. We developed a simulation model for CCD and CMOS imager-based luminescence detection systems. First the photon flux generation process from luminescence probes using ATP-based and luciferase label-based assay kinetics is modeled. An optics simulator is then used to compute the incident photon flux on the imaging plane for a given photon flux and system geometry. Subsequently, the output image is computed using a detailed image sensor model. To validate the model, we developed an experimental CCD-based system that emulates the integrated CMOS-based platform.

We identified a set of applications including nucleic acid, protein and pathogen detection that require 1-1000 assay sites each of size 150x150μm^2, and have reaction times of 1-30s with a minimum emission rate of 10^{-6}lux. As off-the-shelf CCD and CMOS imagers cannot satisfy these requirements, we designed and fabricated a detection SoC. The chip comprises an 8x16 pseudo-differential pixel array, 128-channel 13b ADC and column-level DSP and is fabricated in a 0.18µm CMOS process. Detection of photon flux below 10^{-6} lux at 30s integration time is achieved by directly coupling the target assay to the photodetector sites, the use of low noise circuits, high resolution ADC, on-chip averaging and background subtraction, and correlated multiple sampling.

Submitted to SPIE Boston (Sept. '89) Andrade

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-1 SPIE 89

EVANESCENT-WAVE COUPLING OF FLUORESCENCE INTO GUIDED MODES: FDTD ANALYSIS

D. Christensen*†, J. Andrade†, J. Wang†, J. Ives†, and D. Yoshida*
*Dept. of Electrical Engineering and †Dept. of Bioengineering
University of Utah, Salt Lake City, Utah 84112 USA

ABSTRACT

Since the penetration depth of the evanescent portion of a guided optical mode is on the order of a wavelength, it is possible to design sensors which possess sensitivity to chemistry only within that distance at their surface. An example is the fiberoptic fluorescent immunosensor, which has antibodies immobilized on its surface and the attached antigen concentration is detected by evanescent excitation and collection of the antigen fluorescence via guided modes in the fiber.

A key question in comparing the optical efficiency of this type of sensor to more conventional bulk techniques is the amount of total emitted fluorescence which is collected and guided by the fiber modes. The mathematical analysis of even a simple model of this problem by traditional techniques is complicated; modeling inhomogeneous fluorescent layers on the sensor's surface becomes even more complex.

We have applied a newly developed technique, the Finite Difference Time Domain (FDTD) method, to this problem. In essence, this method numerically solves Maxwell's equations as a function of both space and time for a region of varying permittivities. Included in the two-dimensional model are the waveguide region, the outside bulk region, and a layer of possibly incomplete and inhomogeneous fluorescent sources on the surface of the waveguide. The fluorescent sources are treated as electric dipoles, and the ratio of emitted power that is guided by the waveguide (at moderately far distances from the sources) to the total power radiated is calculated by the analysis. Results show that the local environment of the fluorescent sources has an appreciable influence on the percentage of light coupled into the guide.

Chri -1
Waveguides

ANALYSIS OF EFFICIENCY OF FLUORESCENT COUPLING IN GUIDED-WAVE IMMUNOSENSORS

D. Christensen*† and J. Andrade†
*Dept. of Electrical Engineering and †Dept. of Bioengineering
University of Utah, Salt Lake City, Utah 84112 USA

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ABSTRACT

Optical immunosensors which excite and collect fluorescence via the guided modes of an optical waveguide offer enhanced surface selectivity due to the restricted range of penetration of the evanescent tail of the optical modes into the analyte medium. Such penetration depths are typically on the order of a fraction of a wavelength (2000-3000 A°). A question of major importance in the understanding of this configuration is the efficiency with which the flourescence is excited and, in turn, collected by the optical modes. Ray theory is of little help here since it predicts no interaction between fluorescent molecules above the surface of the guide and the guided modes.

We have used a new numerical technique called the Finite Difference Time Domain (FDTD) method to analyze this optical arrangement. The waveguide is modeled as a rectangular region of higher refractive index surrounded by lower index regions, and the fluorescent molecules are modeled as oriented electric dipoles above the waveguide surface. FDTD allows the computer solution of Maxwell's electromagnetic equations as a function of both space and time, and is valid for near fields (evanescent tails, as in our case) as well as for far fields. We employed a three-dimensional version of the program.

Efficiency of collection is defined as the percentage of total emitted power that is captured by the guided modes of the waveguide. Our analysis shows a collection efficiency which varies from a few percent to above 10% depending upon the geometry of the guide, the number of modes, and the distance of the fluorescent sources above the guide's surface. Excitation efficiencies are expected to be similar, based upon the principle of reciprocity.

Biosensors 90 : First World Congress on Biosensors, May 2-4, 1990

Chri -1
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University of Utah, Salt Lake City, Utah 84112 USA

Biosensors 90

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A SIMPLE EX-VIVO PLATELET RETENTION TEST FOR THE EVALUATION OF MATERIALS BLOOD COMPATIBILITY.

D. L. Coleman*, J. D. Andrade and D. J. Lentz*
University of Utah, Salt Lake City, Utah

The ultimate success of any material designed to interface with blood depends on in vivo performance. Numerous in vivo, ex-vivo and in vitro blood compatibility tests have been described. In general, in vivo tests are relatively expensive, subject to a high degree of technical failure, and incorporate many uncontrolled variables. In vitro methods have been criticized because of poor correlation with in vivo results.

The ex-vivo system described in this paper is an adaptation of the glass bead platelet retention test currently used in clinical hematology to aid in the diagnosis of Von Willebrand's disease. Blood is shunted from the carotid artery of a New Zealand White Rabbit at a known rate of flow through a known surface area and geometry of glass beads. Platelet counts of inflow and outflow blood samples are used to determine the percentage of platelets retained by the test material. Glass beads coated with various polymers or otherwise surface altered can then be compared to the untreated glass beads.

Results to date indicate a species difference for the same material tested in the calf and the rabbit. The effect of flow rate has been evaluated. Data showing materials differences will be presented along with a brief review of current in vivo, ex-vivo and in vitro blood compatibility tests. The potential of this experimental model for the evaluation of other clotting factors related to materials success in the vascular system will be discussed.

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ABSTRACT REPRODUCTION FORM

PLATELET RETENTION OF ALBUMINATED GLASS BEADS

Dennis L. Coleman and Joseph D. Andrade,
Materials Science Division, University of Utah,
Salt Lake City, Utah 84112.

The nonthrombogenic nature of albuminated surfaces has been described. We have evaluated albumin from different species, various purities of albumin, and glutaraldehyde cross-linked albumin. The test system used in this study is an ex vivo modification of the glass bead platelet retention test used to aid in the diagnosis of Von Willebrand's disease. The drop in the platelet count across the test chamber was used to determine the percentage of platelets retained by test materials. Results to date indicate that albuminated glass beads demonstrate significantly ($p>.001$) less platelet retention than untreated glass beads and that, for the time intervals studied, glutaraldehyde cross-linked albumin adheres less platelets than adsorbed albumin. Crystalline albumin retains fewer platelets than fraction V albumin from the same species, 9.9% and 15.4%, respectively. The potential of this experimental model for the evaluation of blood-materials interactions will be discussed.

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CALCIFICATION OF LONG TERM ARTIFICIAL HEART IMPLANTS

D.L. Coleman, A.B. Pons, T. Kessler, J.D. Andrade and W.J. Kolff

Division of Artificial Organs, Department of Surgery, Department of Bioengineering, University of Utah, Salt Lake City, Utah 84112, U.S.A.

Calcification of the pumping diaphragm of long-term artificial hearts implanted in calves is consistently seen in animals surviving over 120 days and is occasionally seen in animals surviving as little as 47 days. Calcium phosphate deposits are tenaciously attached to the pumping diaphragm and appear as discrete plaques. The heaviest deposits are associated with permanent-set creases in the diaphragm material. Both Avcothane-51• and Biomer• fabricated as smooth surfaces exhibit calcinosis.

Although the housing portion of the heart is made of the same material as the pumping diaphragm, calcium deposits have not been seen on the housing. Scanning electron microscopy coupled with X-ray microanalysis has been used to confirm the presence of calcium and phosphorous. Elemental maps for calcium suggest that bubble defects in the diaphragm may act as the initiating site for plaque formation. Such defects combined with the mechanical stress of the pumping diaphragm provide an environment conducive to plaque development. Thrombus deposition is only occasionally seen in calcified areas. However, calcification seen prior to 120 days is seen in conjunction with thrombus induced by particulate contanimants (usually fibers). This suggests the possibility that more than one calcification mechanism may be involved.

Heat inactivated serum has been used to study this problem in vitro (1). Preliminary results using bovine, human, and sheep serum suggest species differences but do not eliminate human serum from involvement in calcium phosphate deposition on smooth Avcothane•, Biomer• and other test materials.

The most immediate solution to prevention of dystrophic calcification may be treatment with diphosphonates (2). Understanding the mechanism of calcification should provide additional solutions to this potential problem with long term pumping bladders.

References:

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(2) Francis, M.D., Centnef, R.L., J. Chem. Ed., 55 (1978) 760

Acknowledgement:

This work was supported by NIH Grant HL 13738-09.

Abstracts, World Biomaterials Congress, April 8-12, 1980

IN VITRO BLOOD-MATERIAL INTERACTIONS: A MULTIPARAMETER APPROACH

Ab-Cole-4

D.L. Coleman and J.D. Andrade

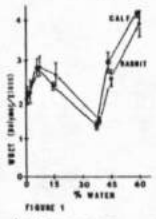
Department of Bioengineering, University of Utah, Salt Lake City, Utah 84112 U.S.A.

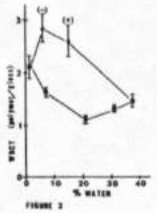
The importance of surface and interface characteristics in blood-material interactions has been the subject of much controversy. This controversy is partially the result of a lack of characterization of materials and partly due to the lack of standard test methods for blood-materials evaluation (1, 2). This study was designed to test three currently popular hypotheses of blood compatibility using well characterized model surfaces and simple in vitro blood evaluation methods.

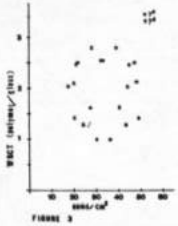
The hydrophilic/hydrophobic ratio hypothesis (3) and the interfacial free energy hypothesis (4) were evaluated using copolymers of hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA). The negative charge hypothesis popularized by Sawyer et al. (5) was tested using copolymers of HEMA and MMA with negatively charged methacrylic acid (MAA) or positively charged dimethyl amino ethyl methacrylate methyl chloride (DMAEMA) and also a copolymer of n-butyl methacrylate and MAA.

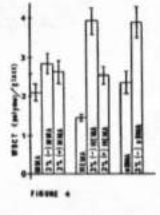
Surface characterization includes air-water and octane-water contact angles of fully hydrated materials, streaming potential measurements and bulk water content data. Blood evaluation includes whole blood clotting times (WBCT) of polymer coated tubes, measurement of partial thromboplastin time, prothrombin time and Stypven time on whole blood exposed to test surfaces and platelet adhesion measurements of test materials.

Results using calf and rabbit blood suggest that the two species give identical whole blood clotting times if test results are normalized to the glass controls for each animal tested (Figure 1). Although WbCT is greatly affected by water content (Figure 2), there does not appear to be a correlation with interfacial free energy. However, there is a complex correlation with the polar and dispersion components of surface free energy and WBCT (Figure 3). The addition of either a positive or negative charge significantly prolonged coagulation in all materials tested (Figures 2 and 4).









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CALCIFICATION OF LONG TERM ARTIFICIAL HEART IMPLANTS

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Calcification of the pumping diaphragm of long-term artificial hearts implanted in calves is consistently seen in animals surviving over 120 days and is occasionally seen in animals surviving as little as 47 days. Calcium phosphate deposits are tenaciously attached to the pumping diaphragm and appear as discrete plaques. The heaviest deposits are associated with permanent-set creases in the diaphragm material. Both Avcothane-51• and Biomer• fabricated as smooth surfaces exhibit calcinosis.

Although the housing portion of the heart is made of the same material as the pumping diaphragm, calcium deposits have not been seen on the housing. Scanning electron microscopy coupled with X-ray microanalysis has been used to confirm the presence of calcium and phosphorous. Elemental maps for calcium suggest that bubble defects in the diaphragm may act as the initiating site for plaque formation. Such defects combined with the mechanical stress of the pumping diaphragm provide an environment conducive to plaque development. Thrombus deposition is only occasionally seen in calcified areas. However, calcification seen prior to 120 days is seen in conjunction with thrombus induced by particulate contanimants (usually fibers). This suggests the possibility that more than one calcification mechanism may be involved.

Heat inactivated serum has been used to study this problem in vitro (1). Preliminary results using bovine, human, and sheep serum suggest species differences but do not eliminate human serum from involvement in calcium phosphate deposition on smooth Avcothane•, Biomer• and other test materials.

The most immediate solution to prevention of dystrophic calcification may be treatment with diphosphonates (2). Understanding the mechanism of calcification should provide additional solutions to this potential problem with long term pumping bladders.

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Abstracts, World Biomaterials Congress, April 8-12, 1980

IN VITRO BLOOD-MATERIAL INTERACTIONS: A MULTIPARAMETER APPROACH

Ab-Cole-4

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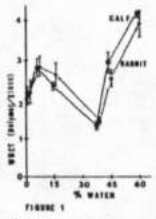
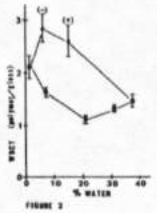
The importance of surface and interface characteristics in blood-material interactions has been the subject of much controversy. This controversy is partially the result of a lack of characterization of materials and partly due to the lack of standard test methods for blood-materials evaluation (1, 2). This study was designed to test three currently popular hypotheses of blood compatibility using well characterized model surfaces and simple in vitro blood evaluation methods.

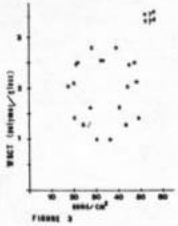
The hydrophilic/hydrophobic ratio hypothesis (3) and the interfacial free energy hypothesis (4) were evaluated using copolymers of hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA). The negative charge hypothesis popularized by Sawyer et al. (5) was tested using copolymers of HEMA and MMA with negatively charged methacrylic acid (MAA) or positively charged dimethyl amino ethyl methacrylate methyl chloride (DMAEMA) and also a copolymer of n-butyl methacrylate and MAA.

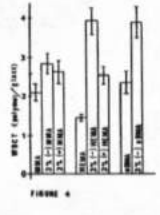
Surface characterization includes air-water and octane-water contact angles of fully hydrated materials, streaming potential measurements and bulk water content data. Blood evaluation includes whole blood clotting times (WBCT) of polymer coated tubes, measurement of partial thromboplastin time, prothrombin time and Stypven time on whole blood exposed to test surfaces and platelet adhesion measurements of test materials.

Results using calf and rabbit blood suggest that the two species give identical whole blood clotting times if test results are normalized to the glass controls for each animal tested (Figure 1). Although WbCT is greatly affected by water content (Figure 2), there does not appear to be a correlation with interfacial free energy. However, there is a complex correlation with the polar and dispersion components of surface free energy and WBCT (Figure 3). The addition of either a positive or negative charge significantly prolonged coagulation in all materials tested (Figures 2 and 4).









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With best regards,
Daniel J. Schneck, Ph.D.

ADSORPTION OF LOW DENSITY LIPOPROTEINS TO BIOMEDICAL POLYMERS

The area of blood-lipid interaction with biomedical polymers has not been clearly defined. The purpose of this dissertation was to examine the interaction of the blood lipid, low density lipoprotein (LDL), with a select group of biomedical polymers. The adsorption characteristics of LDL were studied on filler-free poly(dimethyl siloxane) (PDMSO-FF), Biomer, Cardiomat 610, Kraton 1650, poly(hydroxy ethyl methacrylate) (PHEMA) and glass as the control material. The low density lipoprotein was chosen because of its high cholesterol and cholesterol ester content which related to past *in vitro* studies showing steroidal lipid absorption. Low density lipoprotein was also chosen because of its pathophysiological role in atherogenesis.

The data from this study suggest that LDL adsorption to polymer surfaces can occur by both electrostatic interactions and apolar or hydrophobic interactions. Adsorption of LDL to charged hydrophilic glass control surfaces occurred rapidly, reaching plateau concentrations within a minute. Adsorption of LDL to polymer surfaces appeared to be dependent upon both the polymer hydrophobicity (or apolar nature) and to its flexibility (or dynamic nature) at the interface. Increased surface

concentrations of LDL were observed for both hydrophobic and flexible polymer (Biomer versus PHEMA). Temperature was also found to enhance significantly the surface concentration of adsorbed LDL at 37°C versus 25°C. This was suggested to be due to the core lipid phase transition at 36°C.

Preliminary competitive adsorption studies of LDL with albumin and serum suggest that LDL adsorption occurs rapidly and preferentially. Preliminary studies on the role of LDL in calcification were not conclusive.

The conclusions from this study suggest that LDL adsorption occurs as a function of polymer hydrophobicity, flexibility, and temperature. Further studies are necessary to define the role of LDL in lipid absorption, materials compatibility and calcification in affecting the material integrity in an *in vivo* environment.

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December 1983
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THE STRUCTURE AND PHYSICAL PROPERTIES OF PYROLYZED POLYIMIDE

Polyimide was pyrolyzed in an argon atmosphere at various temperatures and times, and thermally converted to amorphous carbon films. The irreversible evolution of polyimide under progressive heat treatment is characterized by three successive structural changes: pyrolysis, carbonization and graphitization.

The polyimide starts to dissociate at pyrolysis temperatures above 500°C. At temperatures higher than 650°C most functional groups of polyimide decompose to evolve CO, CO_2, H_2 and N_2 gases which are released from the sample. The polyimide then gradually becomes more carbon-rich. It is believed that at pyrolysis temperatures higher than 650°C the polyimide starts to form heterocyclic structures with some oxygen and nitrogen incorporated into the heterocyclic carbon rings. The structure rearranges or recombines to form larger and denser heterocyclic networks at temperatures higher than 700°C, causing an increase of electrical conductivity. This conclusion is supported by the ESCA and conductivity data. Raman, ESCA valence band and X-ray data indicate that the polyimide at pyrolysis temperatures less than 1000°C is amorphous carbon and no long-term periodic structure can be detected. But at pyrolysis temperatures higher than 2000°C, the polyimide is converted to microcrystalline graphite.

Two forms of polyimide were used in this work: Kapton, a fully cured polyimide film, and PI-2525, an uncured polyimide solution. The Kapton film was placed between two quartz plates during pyrolysis; the resulting polyimide is flat, has uniform conductivity, has high chemical resistance, and shows better mechanical strength than Kapton pyrolyzed in free standing conditions. The PI-2525 was spin-cast on different substrates and cured at 200°C. The pyrolyzed PI-2525 polyimide was supported by the substrate.

The pyrolyzed polyimide is stable in air and has reasonable conductivity. Compared with other conducting polymers, pyrolyzed polyimide can withstand rela-