Diagnostic Imaging Applications

Edwin S. Beckenbach
Chairman/Editor

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DIAGNOSTIC IMAGING APPLICATIONS

SPIE Volume 516

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INTRODUCTION

An easily visible trend in medical practice over the last few decades has been the increasing specialization of physicians. By and large, this has been a reasonable response to an astounding increase in information available relevant to the human condition, limiting the field of which even the most encyclopedic mind can have total understanding.

A part of this information overload has been due to sophisticated instrumentation. More and more, the engineer (responsible for the proper design and function of a black box) and the clinical physician (responsible for the proper use of the black box, and for the interpretation of data resulting from this use) have little in common. Each of them is increasingly a layman in the other's field.

Regardless of this situation, or maybe because of it, it is more important than ever that engineers have an understanding of the future needs of clinical and research medicine, and that physicians know something about probable future developments in instrumentation capabilities. Only by maintaining such a dialogue can the most effective application of technological advances to medicine be achieved.

This workshop attempted to provide this kind of information transfer in the limited field of diagnostic imaging. Research physicians, aware both of the limitations of current methodologies and of the potentials of new imaging techniques, were called upon to point out future needs of diagnostic medicine, while instrumentation scientists and investigators explored how these needs can best be met.

It is fair to say that the vigor and speed with which computerized tomography exploded onto the medical scene was not fully anticipated by anyone. It is moot whether the diagnostic benefits from this technology or the social and economic problems arising from its use have generated more interest. And yet, magnetic resonance, and much more complex technology, is poised to repeat this history.

It is hoped that communication devices such as this workshop can contribute to easing transitions to new technologies and to assuring their most effective use.

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DIAGNOSTIC IMAGING APPLICATIONS

SPIE Volume 516

Contents

From Mars to Man: Biomedical Research at the Jet Propulsion Laboratory

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Abstract

In the course of the unmanned exploration of the solar system, which the California Institute of Technology's Jet Propulsion Laboratory has managed for NASA, major advances in computerized image processing, materials research, and miniature electronics design have been accomplished. This presentation will show some of the imaging results from space exploration missions, as well as biomedical research tasks based in these technologies. Among other topics, the use of polymeric microspheres in cancer therapy will be discussed. Also included are ceramic applications to prothesis development, laser applications in the treatment of coronary artery disease, multispectral imaging as used in the diagnosis of thermal burn injury, and some examples of telemetry systems as they can be involved in biological systems.

Introduction

The Jet Propulsion Laboratory (JPL) is located in the foothills of the San Gabriel mountains north of Pasadena, California. Although JPL is officially an operating division of the California Institute of Technology, also located in Pasadena, the vast bulk of the work carried on at the Lab since 1958 has been under contract to the National Aeronautics and Space Administration (NASA). Caltech has the responsibility of administering this contract.

Shortly following NASA's formation, in 1958, JPL was given the job of managing the United States efforts in the scientific unmanned exploration of the solar system, a charter which continues to the present time.

An important part of the legislation that estabilshed NASA was a mandate that NASA take all possible steps to ensure that technological advances and developments resulting from space exploration be applied to improve the condition of man on earth. To this end, JPL, and all other NASA centers, have active technology transfer programs, so that the private sector can benefit from all aspects of the space program.

In particular, applications of appropriate technology to clinical medicine began at JPL in 1965. Since that time the Biomedical Research Program has grown to encompass over twenty separate tasks. These are largely in the areas of automated image analysis, materials applications, and miniaturized electronics.

Images from space

Among its other responsibilities, JPL receives and analyses data from many spacecraft on missions of exploration and discovery through the solar system. A part of this immense mass of data can be reconstructed into photographs showing at close range details of the planets and their satellites.

Foremost among the missions returning such data have been Viking, which explored Mars both from an orbiting spacecraft and from an unmanned lander, and two Voyager missions, which so far have provided data from fly-bys of Jupiter and Saturn, and which are on their way to the outer planets.

JPL Biomedical Research

In the course of this workshop, other presenters will discuss several of the image processing tasks being carried on at JPL within the Biomedical Research Program. I will briefly touch on several research efforts in other areas.

Immunomicrospheres

Researchers at JPL have, over the past ten years, developed methods for synthesizing small (three to ten micron) monodispersed beads from many polymeric materials. Other materials, for instance magnetic particles, can be incorporated into the microspheres. If these microspheres are then "tagged" with suitable antibodies, many applications in biology and medicine become possible.

For instance, continuing advances in production of monoclonal antibodies allows ever greater specificity in antibody/antigen reactions. By using a proper antibody to attach magnetic immunomicrospheres to a particular type of cell, a simple magnetic procedure can be used to separate subpopulations of cells that appear identical to most other separation techniques.

In another application, which has been developed in London, England, and used successfully in over twenty cases, magnetic microspheres treated with antibodies specific to neuroblastoma cancer cells have been used to "cleanse" bone marrow extracted from patients undergoing radiation therapy or chemotherapy. This bone marrow, now free from cancer cells, can be reinjected into the patient following therapy, allowing his immune system to continue operating during the recovery period.

Ceramic hip joint prothesis. A cermet (ceramic/metalic material) developed for use in rocket nozzles is being adapted for use in hip joint replacements. This material, called SIALON for its constituents, silicon, aluminum, oxygen, and nitrogen, is extremely hard and inert, offering excellent wear characteristics and biocompatability. Techniques have been developed so that during manufacture of the prothesis, which is to be used as a femoral cap, the exterior of the ball is extremely smooth, while the interior is porous. This will allow minimal wear against either the natural acetabulum as a high density plastic insert, while allowing bone ingrowth to anchor the prothesis to the head of the femur.

Hip joint biotelemetry. In a related effort, an entire telemetry system has been developed to fit into the hollow head of a standard femoral spike hip prothesis. The purpose of this JPL effort is to collect in vivo data guantifying loads and forces on a human hip as an individual goes about his normal daily activities. These data will then allow future protheses to better survive the stresses of everyday life.

To avoid weaknesses in previous designs, the JPL instrumented prothesis relies on induced power both for the functioning of the transducers and for data transmission. This power is induced through a cuff worn around the thigh and received by an antenna fabricated into the stem of the prothesis. Thus, there are no batteries within the prothesis, and no percutaneous wires. Data can be collected in this way for as long as is desired; when data are not being obtained, and following the experimental period, the prothesis will function in a perfectly "ordinary" way.

Thermal burn analysis. A limiting factor in the prompt treatment of burn injuries is the inability to reliably distinguish between partial thickness burns and full thickness burns. In the former case, sufficient epithelial elements remain to allow spontaneous skin repair; in the full thickness burn those elements have been destroyed. In most cases of full thickness burns, therefore, surgical intervention is necessary, and is best carried out as soon as is practical. Currently, even though many diagnostic aids are available, the only positive method for determining areas of full thickness burn injury is to wait four to six weeks for natural healing processes to indicate necrotic tissue.

In seeking a method for the early determination of deep coagulation and therefore of full thickness burn, infrared photography was considered as a potential method to indicate the devascularization and thermal denaturation associated with the full thickness burn. Deoxygenated blood has a moderate absorptance in the very near infrared.

One may therefore reason that infrared patterns of thrombosed or coagulated venous structure, occurring in zones of stasis or coagulation, could be an indication of full thickness burn. This is because the venous structure capable of detection by infrared photography occurs at dermal depths associated with the cellular elements necessary for spontaneous regrowth of the skin. Typical penetration of the infrared is 2-5 mm through the skin. This would coincide with the base of the hair follicles and the plexus of vessels which, if containing thermally denatured red cells, would be a direct indication of destruction of the basal cells surrounding the root of the hair follicle. These are the deepest elements available for the spontaneous healing of the skin, should total thermal destruction occur above them.

The colorimetry of the burn wound also held suggestions of other spectral areas of potential interest. The zone of hyperaemia, appearing bright red, suggested the use of a region within the red spectrum. The zone of stasis, tending to be a parchment-white, suggested the use of a color not normally appearing on healthy or thermally injured skin since a high spectral reflectance would occur in the zone of stasis. A filter in the green spectrum was chosen.

The analytical approach thus consisted of using infrared light, which penetrates deepest, to investigate the thermal denaturation of the superficial arterioles and venules for indications of a full thickness injury; red light, which does not penetrate as deep as

infrared, for characterizing zones of hyperaemia; and green light, which is the least penetrating, to differentiate the zones of stasis from those of coagulation and hyperaemia, as well as from normal skin.

By making use of these properties of images taken in various wavelengths of light, and combining them in a computer, an image may be produced by the burn site with pseudo-color added to show the extent of injury across the burn. This picture can then be used by the physician to guide his decisions as to required therapy.

Aseptic fluid transfer system. Lack of a proven way to transfer blood from its original container while maintaining sterility is responsible for wasting a large percentage of the blood collected yearly in the United States. Due to the possibility of contamination, the Food and Drug Administration requires that frozen blood must be used or discarded within a few hours at thawing. Particularly in neonatal surgery, this means that only a few tablespoons out of a bag may be used, with the rest wasted.

Using plastics developed for space use, JPL has devised a system to overcome this problem. The basic system consists of two flat tabs, each approximately 3 cm x 6 cm. Each of these tabs is made of two sheets of plastic, sealed around the edges, with a length of small diameter plastic tubing exiting this sandwich from one of the narrow ends. The operation of the system relies on the fact that within each tab, the plastic used for one side has a much lower melting point than that used for the other side. The last element in the system is a sealing device consisting of movable jaws upon which is embossed a raised platen in the shape of an "H".

If, then, two tabs are placed together so that the lower melting point faces are in contact, and this assembly is then placed between the jaws of the sealing device, which is then heated to an appropriate temperature and closed with the proper pressure, a passageway is created from one tab to the other, and hence, from one tube (the input) to the other (the output). The choice of plastics can be made in such a way that the heat necessary to form a seal around the passageway is sufficient to also sterilize the area involved.

With a little imagination, it should be clear that different configurations of single or multiple tabs can be made to allow any combination of transfers and resealings, all with the sterility of the original material maintained.

In addition to blood use, this system can be used with any liquids where sterile conditions must be considered. The concept has been patented and licensed to a medical devices manufacturer, and should be in use by the end of 1985.

Hydrocephalus shunts. Hydrocephalus is a condition wherein cerebrospinal fluid produced by the ventricles of the brain is unable to drain from these cavities, resulting in high pressures on the brain tissue. If the condition develops in utero, sufficient pressure can occur to prevent normal brain tissue growth, leading to severe mental retardation.

Treatment for hydrocephalus, both in children and also in the fetus, consists of insertion of a shunt into the ventricular cavity, thus draining the excess fluid and preventing pressure buildup. Typical shunts are made of silastic tubing approximately 2 mm in diameter, with eight to twelve holes in the distal one cm for carrying the fluid into the lumen of the tubing, and thence, out of the cranium. There is, however, a cellular component of cerebrospinal fluid that will clog these holes both by simple mechanical means and by growing into the lumen. Of these mechanisms, cellular ingrowth is the more difficult to deal with.

By using ion beams developed for propulsion systems, JPL engineers have been able to produce, not a dozen or so large holes, but up to 6000 holes in the distal centimeter of the shunt catheter. These minute perforations, as small as 10 microns in diameter, inhibit cell ingrowth and lengthen the service time of the implant. The efficacy of this approach has been shown in animal models and shunts based on this design should soon be available for human use.

Laser angioplasty. Atherosclerotic cardiovascular disease causes more deaths than all other diseases combined. The disease affects both the heart and peripheral blood vessels. According to the Department of Health and Human Services, 2.5 million Americans have diagnosed coronary heart disease, and at least an equal number have life threatening, but undiagnosed disease. In practical terms, roughly 10% of the adult population over 40 has coronary artery disease. Five hundred thousand of these individuals will die of the disease this year. An additional 3 million Americans have peripheral vascular disease requiring therapy.

As a result, more health dollars in the United States are spent on atherosclerotic

cardiovascular disease for diagnosis and for treatment than any other disease. For coronary disease, these numbers were last compiled in 1979. At that time, the total cost to the health care system was 29.8 million dollars per year. A significant component of this cost is for surgical therapy. In 1981, there were 159,000 coronary artery bypass surgeries and 512,000 peripheral vascular procedures performed in the United States.

There are two alternative therapies for atherosclerotic vascular disease. One, balloon angioplasty, is now becoming established; the other, laser ablation, is just emerging. In balloon angioplasty the surgeon attempts to decrease the magnitude of vessel obstruction by inflating an intravascular balloon, crushing the obstruction into the vessel wall. Although crude, the procedure is often initially successful. There is, however, a significant complication rate: 1% of the patients die during the procedure, and 5% have a complication requiring emergency heart surgery. About 40% of the vessels treated subsequently re-obstruct at the original location.

Laser surgery is an emerging therapeutic alternative. In December 1981, it was first reported that atherosclerotic plaque could be vaporized by laser irradiation. A fiberoptic laser catherter has been used to successfully remove atheroma from coronary and femoral arteries in cadavers. Nevertheless, there are important problems. Several investigators showed that the laser action involved burn injury, which extended to adjacent normal tissue, and often resulted in vessel performation, a potentially catastrophic complication if it were to occur in man.

This laser-induced thermal injury can, however, be eliminated by a process first demonstrated by the Laser Angioplasty research group at Cedars-Sinai Medical Center and reconfirmed in collaborative studies done at JPL, in which ultraviolet excimer laser radiation is employed. Although the exact mechanisms remain to be elucidated, it is possible that the process of multiphoton absorption leads to highly localized electronic products. Instead of a ragged thermal crater created by the explosive transition of tissue to vapor, the ultraviolet laser produces a very sharp incision comparable to that of a scalpel, with no adjacent tissue injury. The clean incision sharply reduces the risk of vessel performation, and provides the critical technologic advance necessary for development of laser therapy of atherosclerotic vascular disease.

Summary

In these and many more investigations, then, JPL is fulfilling its commitment as part of the NASA family to make available to all of us the fruits of the scientific exploration of space. There will always be more problems than solutions, but with the help of dedicated members of diverse disciplines, solutions will be added day by day and year by year.

Even when solutions are not forthcoming, hope can be extended. Over ten years ago, a boy known only as David was born with severe immunological deficiencies that would have killed him within days of exposure to the environment that is harmless to most of us. For that entire decade and more, David was provided sterile isolation through NASA technology. He grew and thrived - at least to whatever extent he could in the absence of most intimate human contact. The search went on to find a solution to his basic disease but was not successful. Earlier this year, in the hope that his system could at least begin to cope with the environment, David was removed from his isolation. Technology extended David's life and offered hope; it could not cure him. David died within weeks. We have a long way to go.

Current and future indications for magnetic resonance in medicine

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Since Nuclear Magnetic Resonance was first used to image the human body in the late 1970's (1), image quality has steadily improved. At this time, image quality from magnetic resonance (MR) imaging, as it is now called, rivals that produced by x-ray computed tomography (CT). The cross-sectional tomographic images of the body produced by magnetic resonance display hydrogen density in the body, modified by the magnetic relaxation times, T1 and T2 (2). In addition to imaging the body, MR can also provide spectroscopic information from a specified region of interest within the body. Spectroscopy gives the concentration of different chemical species of the same chemical nucleus (e.g., P-31, C-13, Na-23), again modified by the magnetic relaxation times. Although such spectra have been obtained from the human body, the role of spectroscopy in clinical medicine has yet to be defined. The following discusses the indications for magnetic resonance imaging in current medical practice relative to existing imaging modalities such as CT. Potential future indications for magnetic resonance (including both imaging and spectroscopic applications) will be discussed.

Current indications for magnetic resonance imaging in medicine

In general, magnetic resonance provides cross-sectional images of the body in any of three orthogonal planes, usually transverse axial, coronal, and sagittal. It does so without hazard to the patient, i.e., without utilizing ionizing radiation such as x-rays or gamma rays. The only patients currently excluded from magnetic resonance imaging are those who have cardiac pacemakers (which may malfunction in the presence of strong magnetic fields), intracranial aneurysm clips (which torque in the magnetic field and may become dislodged from the artery), and patients who are incapable of remaining motionless for the 5-30 minutes required for the examination. At this time, 3000 patients have been scanned at the Huntington Medical Research Institutes in Pasadena, California. 80% of these examinations have been performed for suspected disease of the brain or spinal cord. In a recent comparison of CT and MR in the evaluation of disease in the brain and cervical spinal cord (3), MR was able to detect disease in 30% of the cases where CT was entirely normal. Most of these cases involved multiple sclerosis or lesions involving the cerebellum or brainstem. These structures are located in the posterior fossa at the base of the skull where CT is limited by artifacts arising from the dense bone. In the cervical cord, MR was able to diagnose syringohydromyelia (a cystic degeneration of the cord) where CT was entirely normal.

Multiple sclerosis is difficult to detect by CT especially during the early stages of the disease. The diagnosis by MR is facilitated by the great sensitivity to demyelination and increased water content. MS plaques are easily identified in the periventricular white matter as well as in the white matter of the cerebellum, brainstem, and cervical spinal cord. Other periventricular processes such as deep white matter infarcts and normal and high pressure hydrocephalus are also well evaluated by MR where CT is currently limited. The potential to discriminate obstructive forms of hydrocephalus from hydrocephales ex-vacuo (central atrophy) is particularly important and is a distinction which often cannot be made by CT. The potential ability to diagnosis normal pressure hydrocephalus (which is one of the few treatable causes of dementia) is also quite exciting.

Early diagnosis of subdural hematomas and other extraaxial fluid collections is facilitated by the direct coronal images possible by MR (compared to the axial images avaiable on CT). This is particularly important at the vertex of the skull where small subdural collections can easily be missed by CT.

In the evaluation of sensorineural hearing loss, CT has been shown to be particularly efficacious in the evaluation of bony abnormalities such as cochlear otosclerosis as well as congenital and traumatic abnormalities of the ossicles. A prominent cause of sensorineural hearing loss, however, is the acoustic neuroma. Such tumors are better seen and less invasively evaluated by MR than CT (which may require spinal puncture and injection of air for optimal evaluation). Tumors as small as 4 mm in diameter have been well detected by MR (4).

Arteriovenous malformations and intracranial aneuryms can be seen without injecting contrast. Although MR is very useful to screen for the presence of such vascular

abnormalities and to determine the presence of associated hemorrhage, angiography remains the gold standard in the evaluation and preoperative assessment of such lesions.

At this time, MR is the examination of choice for patients where disease is suspected in the brain. This would include patients presenting with headaches, seizures, or focal neurologic findings. In addition, patients with transient ischemic attacks or mild strokes and patients with known cancer in other parts of the body that may metastasize to the brain should be examined first by MR rather than CT. Although MR is more sensitive in the detection of these diseases, in certain cases it may not be as specific as CT. The subtle tumor calcification which may be present in oligodendrogliomas and astrocytomas is certainly better seen by CT than MR. Meningiomas have a characteristic appearance on CT which includes dense homogenous enhancement following administration of intravenous contrast. The CT appearance is more specific than MR which does not use intravenous contrast at this time. Known tumors which enhance with contrast on CT should also probably be followed by CT rather than MR. Again, since intravenous contrast is not currently available for MR, the ability to define breakdown in the blood brain barrier by using intravenous contrast gives CT an advantage - for now. Paramagnetic contrast material should become available for MR in the near future.

MR has been shown to be quite useful in the evaluation of Chiari malformations and other abnormalities at the base of the skull which involve not only bony structures but the brainstem, cerebellum, and cervical cord. As noted above, MR is useful in the noninvasive evaluation of syringohydromyelia which may be associated with Chiari malformations. A definitive diagnosis can often be made without the necessity of injecting intrathecal metrizimide generally required for CT evaluation.

In addition to the diagnosis of syringohydromyelia, MR is useful in the evaluation of spinal tumors and spinal hemorrhage or edema secondary to trauma. The relationship of the spinal cord to the bony spinal canal is displayed on direct sagittal images and is particularly useful in the evaluation of patients with rheumatoid arthritis where C1-2 subluxation can result in narrowing of the bony canal, compromising the cervical cord.

Although MR is useful in determining degeneration of the intervertebral disk and in some cases in demonstrating disk herniation, CT remains the cross-sectional modality of choice in the assessment of both disk herniation and the sequelae of this process, spondylosis. This is due to the greater sensitivity of CT in the evaluation of the bony and ligamentous hypertropy which are components of spondylosis.

MR is useful in the evaluation of metastatic disease to the spine and disk space infections. MR can be used for the evaluation of spinal dysraphism (spina bifida, meningocele, meningomyelocele, tethered cord, lipoma) without the necessity of injecting intrathecal contrast.

In the evaluation of head and neck tumors, MR is becoming competitive with CT, primarily through its ability to image in the three orthogonal planes. Lymphadenopathy and vascular displacement are well seen by MR.

In the chest, MR is currently limited by respiratory and cardiac motion, although, with cardiac gating, the latter aritfacts can be minimized. MR is useful in the mediastinum in the evaluation of early adenopathy. It is useful in the heart in the evaluation of myocardial hypertrophy, myocardial and pericardial tumors, and pericardial effusions. CT remains the examination of choice for parenchymal abnormalities in the lung since that evaluation generally requires assessment of calcification and must be performed during breath-holding.

In the upper abdomen, MR is currently limited by respiratory motion of the diaphragm. Thus in the evaluation of hepatic, pancreatic, splenic, adrenal, and possibly renal lesions, late generation rapid scanning CT has generally been able to provide better images.

In the pelvis MR is competitive with CT. MR can image directly in the transaxial, sagittal, and coronal planes without using ionizing radiation near the reproductive organs. MR can diagnose intracapsular prostatic carcinoma and distinguish this from benign prostatic hypertrophy (5). Since this is the second most common carcinoma in men, it is of some clinical importance. CT is unable to make the determination of intracapsular disease. In addition, digital evaluation of the prostate has been shown to be both insensitive and nonspecific in the evaluation of early prostatic carcinoma. For this reason, early evaluation of prostatic carcinoma is likely to become a major indication for MR in the near future. Similarly, evaluation of bladder carcinoma, particularly at the base, is facilitated by the ability to perform direct coronal and sagittal imaging. Using MR, it is possible to assess early involvement of seminal

vesicles and perivesicle fat in the evaluation of both prostatic and bladder carcinoma. Early pelvic adenopathy is easily determined since lymph nodes have a much different signal than flowing blood in the iliac vessels. Whether MR will be able to determine neoplastic involvement of nonenlarged lymph nodes remains to be seen, however.

In the evaluation of avascular necrosis of the hips, MR has been shown to be somewhat more sensitive than both bone scintigraphy and CT in early studies. Also, MR is useful in the evaluation of soft tissue and osseous tumors.

Future applications of magnetic resonance in medicine

Although NMR spectroscopy has been used in chemistry and physics laboratories around the world almost 40 years, such techniques have been applied to living systems only in the last decade. Using phosphorous spectroscopy, the relative concentrations of ATP and other energy-related metabolites can be assessed to determine regions of the brain or heart deprived of the usual blood flow and oxygen supply. Similar information may be possible with proton spectroscopy (with identification of the lactate peak) and with direct sodium imaging. These applications require much stronger magnetic fields than are currently used for imaging (i.e., in excess of 1.5 Tesla). In addition, the uniformity of such magnetic fields must be two orders of magnitude better than that specified for magnets currently being used for imaging. For these reasons, the cost of magnets used in NMR spectroscopy is significantly greater than those used for magnetic resonance imaging.

P-31 spectroscopy has been used for the evaluation of tumors being treated with chemotherapy. The effect of chemotherapeutic agents on normal structures can also be assessed. In particular, adriamycin cardiotoxicity may be amenable to spectroscopic evaluation due to the presumed free radical involvement.

Although major advances are expected in magnetic resonance spectroscopy, continued improvements are likely to occur in magnetic resonance imaging. Advances in the RF coils and electronics and the gradient coils and their power supplies will continue to increase the signal-to-noise and decrease the time required for imaging. Similar gains may be achieved at higher magnetic fields. Use of surface coils may improve resolution of superficial structures in clinically reasonable imaging times. Images of the orbits produced using this technique have shown exquisite anatomic detail not available by CT.

Use of respiratory gating should allow the extension of MR to imaging of the upper abdomen where respiratory artifacts are currently a major difficulty. When the diaphragm is immobilized (as it is in patients with pleural effusions or ascites) exquisite images of the abdomen can be obtained which are certainly competitive with CT.

The use of MR contrast agents should extend the applications of MR throughout the body. In the brain in particular, paramagnetic intravascular contrast agents can define breakdown of the blood-brain barrier in much the same fashion as currently shown using iodinated contrast agents in CT. Such agents include gadolinium DTPA and nitroxide free radicals. Although such agents are not currently available for clinical use in the United States, early testing has been performed in Europe with great success. Future linkage of paramagnetic agents to monoclonal antibodies may provide very specific information not available by other imaging techniques.

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High speed quantitative digital microscopy

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Abstract

Modern digital image processing hardware makes possible quantitative analysis of microscope images at high speed. This paper describes an application to automatic screening for cervical cancer. The system uses twelve MC6809 microprocessors arranged in a pipeline multiprocessor configuration. Each processor executes one part of the algorithm on each cell image as it passes through the pipeline. Each processor communicates with its upstream and downstream neighbors via shared two-port memory. Thus no time is devoted to input-output operations as such. This configuration is expected to be at least ten times faster than previous systems.

Introduction

Cervical cancer screening by cell image analysis is a computationally intensive image processing application that does not lend itself well to either conventional, single CPU architecture or to real time raster scan image processing hardware. Array processors are also an inefficient means for implementation.

The processing steps of image segmentation, cell measurement and cell classification require random access to the image and are considerably data dependent. Thus, the single CPU architecture is useful, but frequently too slow to meet performance requirements. Real time raster scan implementations perform some of the steps well, but are inappropriate for others. Since the bulk of the computational load is 8-bit arithmetic, the typical floating point array processor is inefficient because the overhead of data transfer to and from the array processor is as time consuming as simply performing the operations in the host.

One solution to this problem is to use several inexpensive microprocessors all executing simultaneously. The two major decisions that remain are (1) how one should divide the images and algorithms among the CPU's and (2) how one should implement interprocessor communication.

The pipeline processor

For a single purpose system, such as a Pap smear analyzer, one can design the hardware and software simultaneously to arrive at an optimal solution. We have chosen a pipeline multiprocessor architecture with data flow via shared dual-port memory. In this arrangement the processing algorithm is partitioned into sequential steps, and each step is implemented on a separate CPU. The images flow from one CPU to the next, like in an assembly line and emerge from the last one fully processed. Since each CPU shares image memory with its upstream and downstream neighbors, there are no I/O operations. As one CPU writes its output into shared memory it automatically appears for use by the downstream processor.

Figure 1 shows the architecture of the Pap smear analysis system. The host (master) computer handles operator communication and keeps track of the number of normal and abnormal cells found. Each of the identical modules implements one step in the analysis of a cell.

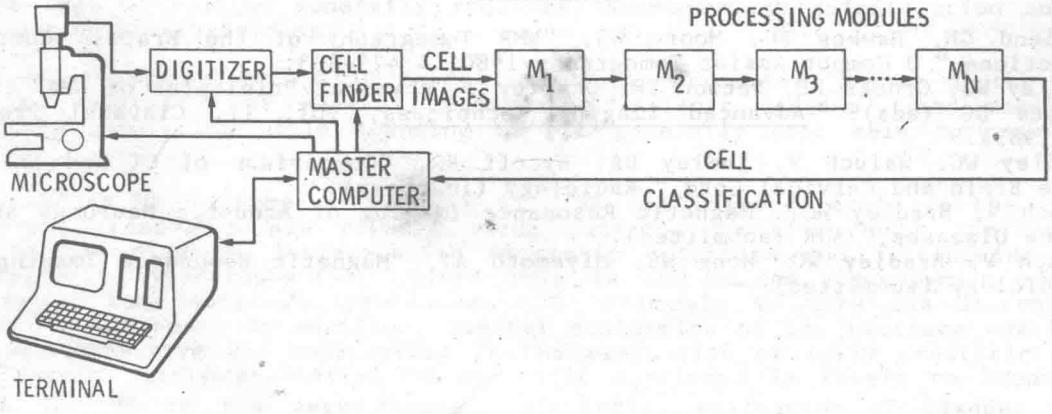

Figure 1 Pipeline architecture

The Pap smear analysis system consists of a microscope with image digitizer, a cell finder circuit to detect the presence of cells in the images, a master or host computer with operator's console, and a series of identical processing modules. Each module performs one step in the analysis and passes the cell image on to the next module. The last module identifies the cell as normal or abnormal. The host tabulates the number of each cell type and reports a diagnosis. It also controls the microscope, digitizer and cell finder and downloads programs into the modules.

The processing modules

Figure 2 shows a block diagram of one pipeline processing module. Each board contains the processor, two input memories and a program memory that can be downloaded from the host. All three RAMs are 64K bytes. An MC6829 memory management chip handles the mapping of the 64K byte address space of the MC6809 into the 2M byte physical address space of the system.

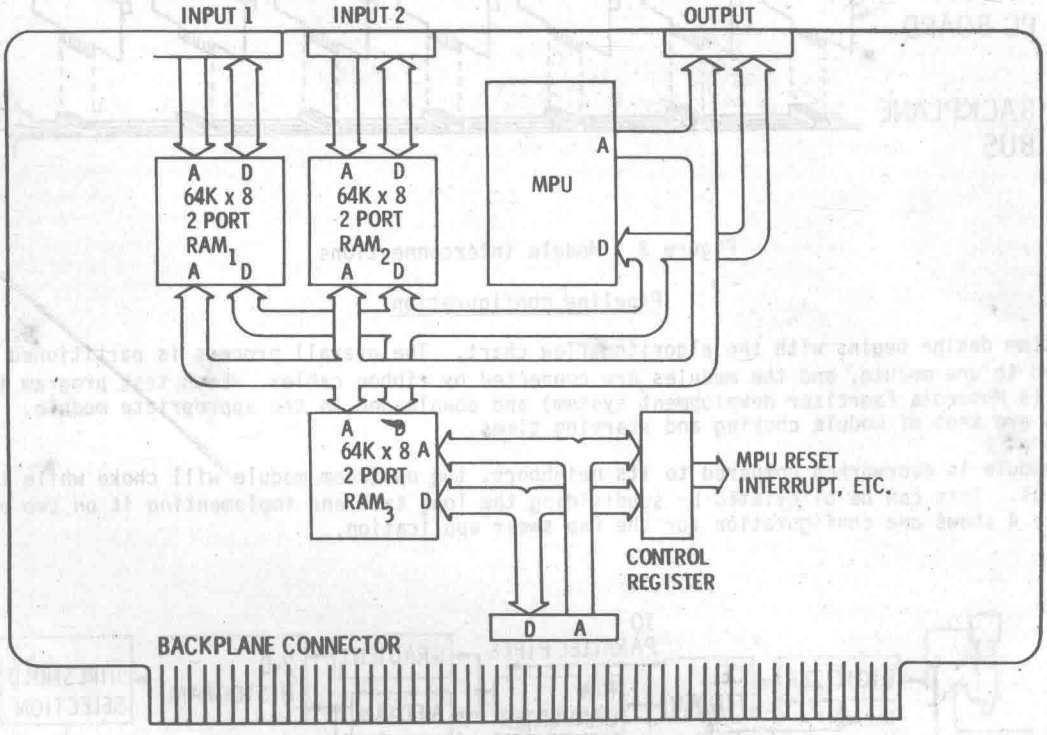

Figure 2 Pipeline processing module

Each processing module is implemented on a single printed circuit board. Each contains the MC6809 microprocessor, and three two-port RAMs, two shared with upstream processors via input connectors, and one shared with the host via the backplane. A control register permits the host to control the MPU. The address bus is expanded to 21 bits by an MC6829 memory management chip. The address and data busses are brought out through ribbon cable connectors so that output data can be stored in downstream modules. For the Pap smear application, image size is fixed at 128 by 128 bytes.

Figure 3 shows how the modules are connected together. The ribbon cable technique allows considerable flexibility in configuring the pipeline, which can be reconfigured simply by changing the cables. The assignment of particular software processes to individual modules must, of course, match the cabling configuration.

The processing modules communicate via ribbon cables connected to the top of the cards. Each module can receive input data from up to two modules and deliver data to as many as thirteen. The host can download program memory and control each module via the backplane bus.

Pipeline operation

Each module operates independently and autonomously. As long as there is an input image from the upstream module available for processing and output memory space available in the downstream module, the program executes. Otherwise it waits for available data or memory. The algorithm partitioning must be done in such a way as to minimize "choking" (no available output memory) and "starving" (no input data) of the pipeline. Since execution times are image dependent, this must be done on a statistical basis. In the development stage, each module keeps track of its choking and starving time so that repartitioning of the algorithm can keep these to a minimum.

The local program can assume input and output arrays are always at the same locations, cell after cell. Furthermore I/O operations as such are never required since the shared memory concept makes one module's output array coincide with another module's input array. The memory management chip takes care of mapping the 64K byte MPU address space into the 2M byte physical address space of the ribbon cable busses.

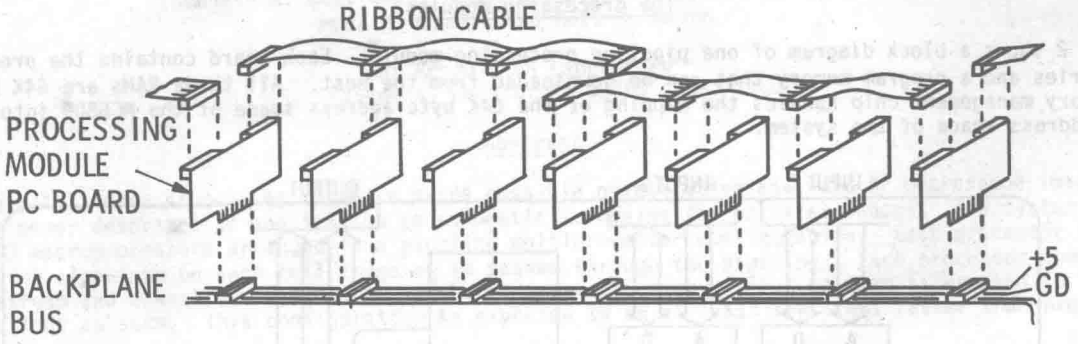

Figure 3 Module interconnections

Pipeline configuration

Each system design begins with the algorithm flow chart. The overall process is partitioned into tasks each assigned to one module, and the modules are connected by ribbon cables. Each task program is developed in the host (a Motorola Exorcisor development system) and downloaded to the appropriate module. During testing, records are kept of module choking and starving times.

If one module is overworked compared to its neighbors, the upstream module will choke while the downstream module starves. This can be alleviated by subdividing the long task and implementing it on two or more modules. Figure 4 shows one configuration for the Pap smear application.

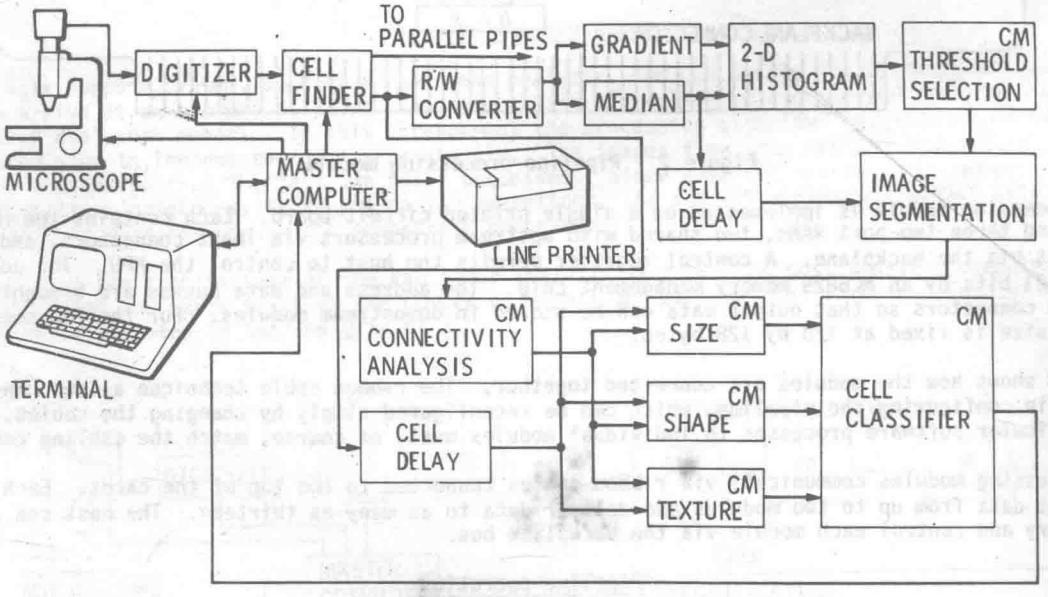

Figure 4 Pap smear configuration

This is one possible configuration of pipeline modules to perform the analysis of cervical cells. Each box represents a pipeline module that performs a specific operation on each cell image that comes through the pipe. Notice that in several instances one module receives data from or delivers data to more than one other module.