Integrated Sensors in Biological Environments*

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Abstract

This paper reviews the application and opera-
tion of integrated sensors and actuators in biolog-
ical and physiological environments. Integrated
transducers are widely employed for invasive and
non-invasive patient monitoring, for recording
and understanding biological events and systems,
for delivery of chemicals and electrical stimuli into
the body, and as a means for eventual realization
of closed-loop visual, auditory and muscular pros-
theses. The state-of-the-art in the development of
precision microstructures, interface electronics
and signal processing, and packaging and encap-
sulation for integrated transducers operating in
biological environments are discussed. The tech-
nologies derived from research on biomedical inte-
grated sensors that have been applied to sensors
used in other application areas are presented.

Introduction

The rapid development of solid-state transduc-
ers over the past two decades has been brought
about in part by the application of integrated
circuit technologies to fabricating precision micro-
structures and devices, and by the great need for
sensors and actuators that can provide the neces-
sary performance requirements that many of to-
day's electronic systems demand. These systems
are being used in a number of application areas,
including transportation, robotics, industrial man-
ufacturing, consumer electronics, and health care.
Among these, health care has been a traditionally
important field of application for solid-state sen-
sors as it not only has some of the most stringent
requirements in terms of performance, size and
reliability, but it also has provided the necessary
resources to carry out some of the fundamental
research and development efforts to realize a vari-
ety of solid-state sensors.

This paper reviews the application of inte-
grated sensors (and actuators) in biological and
physiological environments and discusses the chal-
lenges encountered in their successful deployment.

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First, a brief review of some of the application
areas of implantable integrated sensors in biologi-
cal environments will be given. Next, three major
fields of research and development of integrated
sensors and actuators will be discussed. These
include fabrication of precision microstructures,
incorporation of on-chip interface electronics and
signal processing at the sensor site, and packaging
and encapsulation of the sensor structures for
long-term operation in the body. Finally, conclud-
ing remarks will be drawn discussing the impact
of and results derived from research and develop-
ment efforts on solid-state integrated sensors and
how these efforts have influenced the field of
solid-state transducers as a whole.

Application of Solid-state Transducers in Biological Environments

As solid-state integrated sensors have been re-
duced in size, have become more reliable, and have
come to incorporate on-chip signal processing,
their use as research tools as well as clinical
instruments has been increasingly growing. Solid-
state sensors and actuators find a wide range of
applications in biological environments [1]. They
are often used for invasive monitoring of patients
ranging from simple measurement of electrical and
chemical biological events, such as the recording of
biopotential discharges generated electrochemi-
cally within individual neurons, to recording and
monitoring of physical events. Solid-state actua-
tors are also finding increasing application for
delivering electrical and chemical stimuli to the
body [2]. Eventually, it is hoped that a combina-
tion of sensors and actuators will be used to realize
complete closed-loop control prosthetic systems
that enhance or restore functions for the handi-
capped, as shown in Fig. 1. In such systems, the
sensors derive control signals from the body and
use these signals to generate appropriate stimuli to
induce a desired function in the body. The applica-
tion of the stimuli is adaptively controlled by the
feedback signals provided by the sensors. Once
developed, these systems will find widespread ap-
plication in auditory, visual and muscular prosthe-
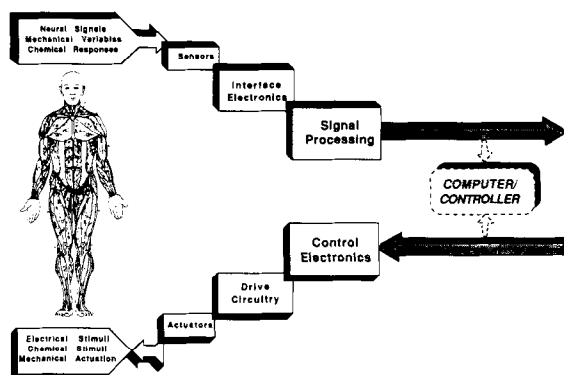ses to restore function to the handicapped [2].

Fig. 1. Diagram of the necessary components for a closed-loop prosthetic system.

Research Efforts on Integrated Sensors and Actuators

The successful development of integrated implantable sensors (and actuators) has depended to a large extent on research and development in three major areas. These include: (i) fabrication of precision microstructures for both mechanical support and transduction; (ii) design and development of electronic circuitry that can interface with the transducers and process the recorded signals for eventual transmission to the outside world; and (iii) development of bicompatible packaging and encapsulation techniques for the long-term protection of implantable sensors in the face of long-term exposure to body fluids, and of techniques for transmission of power and control/data signals to/from the implanted sensor/actuator. This section discusses these issues and illustrates the problems, solutions and challenges through examples of integrated sensors being developed.

Precision Microstructures

The successful realization of practical integrated sensing structures during the past decade has been due in part to the continuing progress being made in integrated circuit process technology in general, and to the successful development of additional processes specifically required for sensors, the most important of which has been silicon micromachining. The ability to micromachine silicon with high precision has enabled the fabrication of a variety of integrated sensors that have found their way into commercial markets. The small size, precise dimensions, and reproducible physical characteristics of solid-state silicon sensors have been the desirable features for most biomedical applications where reducing the implant size is of paramount importance in order to minimize tissue damage. Precision microstructures such as silicon substrate probes, silicon dia-

phragms for implantable pressure sensors, organic membranes for chemical sensors, silicon micro-tools for microsurgery, and (in the future) valves and pumps are but a few of the very many kinds of microstructures that have found biomedical application. These microstructures can be formed using a variety of techniques including orientation-dependent etching, concentration-dependent etching through boron-doping and boron etch-stop techniques, and electrochemical etching of silicon [1]. A number of these structures currently used for biomedical applications are described below.

Figure 2 shows the structure and several views of a silicon microprobe used for multichannel recording and stimulating a variety of biological tissues. The application of IC and silicon micromachining techniques has, for the first time, allowed high-yield fabrication of these structures which have to be very small, be strong and should have reproducible shapes and dimensions. The silicon substrate is formed using deep boron diffusion and etched free from the host substrate in EDP. The microprobe shape can be controlled through the patterning mask and the time and temperature of the boron diffusion step. All of the probe dimensions can be controlled to better than 1 μm. The substrates can be scaled down in width without reducing the thickness, as shown in Fig. 3(a) where an SEM of the cross section of a 16-μm-wide, 8-μm-thick silicon probe is shown. These electrodes are mechanically strong and very flexible, as shown in Fig. 3(b), and can bend to angles larger than 90°. They are physically very small to reduce tissue trauma, are encapsulated with thin films to provide long-term protection against body fluids, and are extremely reproducible in terms of their physical and electrical characteristics [3].

Another commonly used silicon microstructure in a number of biomedical applications is the silicon diaphragm used both for mechanical support and for transduction. For most of these applications two critical requirements, very small size and high performance, have to be satisfied. Deep and shallow boron diffusions together with silicon-glass electrostatic bonding are used to fabricate an ultraminiature capactive pressure sensor for a cardiovascular catheter [4]. The structure of the pressure sensor is shown in Fig. 4, along with a photograph of a fabricated chip. The support rim is formed using a deep boron diffusion and is 12 μm thick, while the diaphragm is formed using a shallow boron diffusion and is ~ 1.5 μm thick. The diaphragm is 290 × 550 μm^2, and the overall chip measures 450 × 700 μm^2. The pressure sensor is mounted in a 0.5 mm OD catheter and can be used for applications such as pressure monitoring
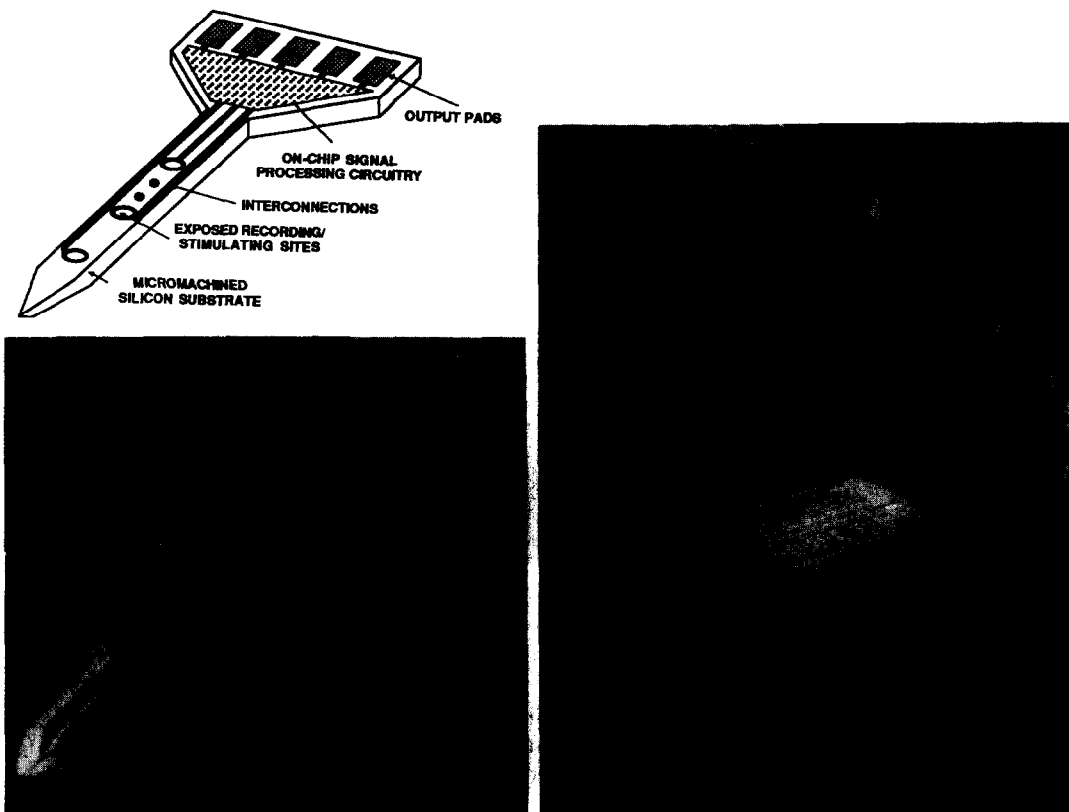
Fig. 2. Structure and several views of silicon microprobes for use in multichannel recording and stimulation.

during angioplasty (balloon pumping). The fabrication process for this sensor is single-sided, very simple, and high-yield. The precision and reproducibility provided by silicon micromachining techniques have allowed the successful fabrication of this structure.

These two examples illustrate the possibilities provided by silicon micromachining, however, one can easily cite many other similar examples where integrated sensors can offer the necessary features often required for biomedical applications. Indeed, these same techniques are being employed to fabricate a whole new generation of devices for drug delivery and for microsurgery [5].

Interface Electronics and Signal Processing

The signals recorded by many biomedical sensors have to be sent out to the outside world for
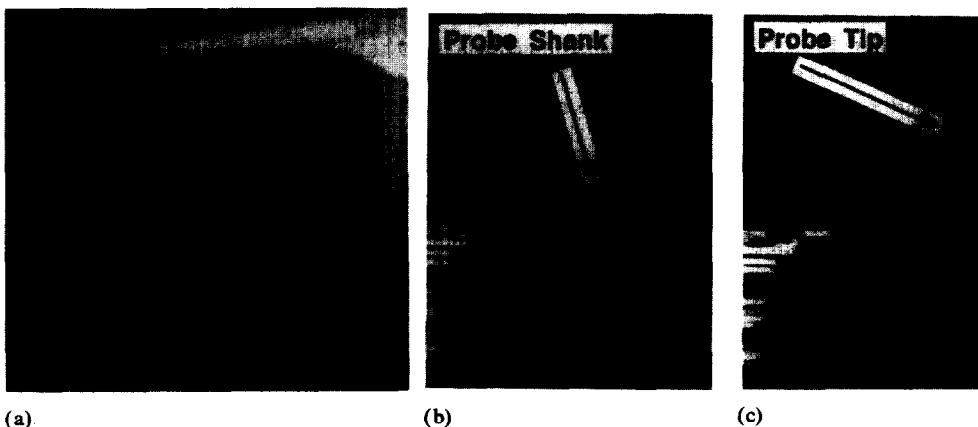
(a)   (b)   (c)

Fig. 3. (a) SEM view of the cross section of a scaled silicon substrate 16 μm wide and 8 μm thick. (b) A two-shank scaled silicon substrate under deflection; the shank is 15 μm thick, 30 μm wide, and about 1.4 mm long.
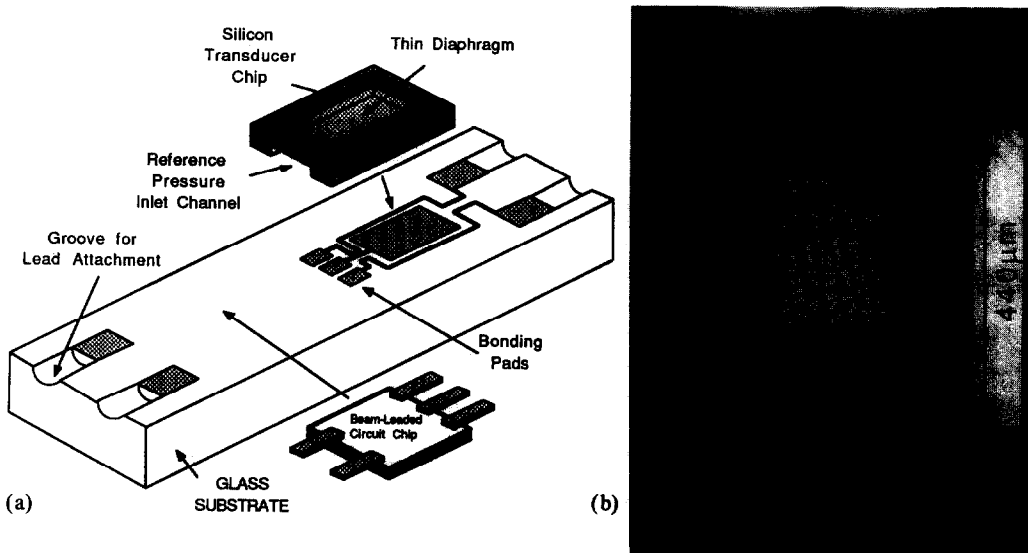
Fig. 4. (a) Structure of a capacitive pressure sensor for a cardiovascular catheter. (b) Photograph of a fabricated ultraminiature sensor; the diaphragm measures $290 \times 550 \times 1.5 \ \mu m^3$.

further processing and storage. These signals are typically very small and the sensor interface typically has a high impedance. In addition, for many implantable transducers it is desirable to record many signals using a single sensor. Therefore, the number of leads that need to be attached to the sensor is typically large. Inclusion of interface electronics and signal processing circuitry at the sensor site (monolithic or hybrid) can help alleviate these problems and serves four main functions: (i) lead reduction; (ii) signal amplification; (iii) output lead buffering; and (iv) data reduction.

Reducing the number of leads is one of the most important functions for the majority of interface circuits used in biomedical sensors. External leads are not only a major source of failure but are also relatively large compared with the sensor structure itself. The number of external leads can be reduced by either multiplexing the recorded biological signals onto a single output lead [3], or by superimposing clock and control signals over the power lines [4].

Amplification of recorded signals is also desirable in many applications where the amplitude of the signal is typically very low (i.e., in the hundreds of microvolts regime). Amplification of these signals at the sensor site before transmission to the outside world enhances the overall signal-to-noise ratio thus reducing the effects of noise from the environment. For many integrated sensors this can be achieved by using MOS and bipolar amplifiers that require only minimal amount of circuitry with nominal gain, bandwidth and performance specifications.

Since many implantable sensors have characteristic impedances that are very high (in the megohm range), it is required that the output leads are buffered to protect against leakage and parasitics in the face of long-term exposure to body fluids. Providing this enhanced drive capability for the output leads is crucial to the long-term stability of the overall sensor structure and simplifies the packaging and encapsulation constraints on the output leads. This function alone can be very helpful for many implanted sensors since the effects of the environment on the output leads are greatly minimized.

Finally, reducing the data processing overhead on the external computers by signal processing at the sensor site will be required for many future implantable sensors. Biological events have a very low bandwidth and it is often not necessary to transmit the full passband to the outside world. For many applications having knowledge of the occurrence of an event or of the frequency of the occurrence of an event is all that is needed. In these applications it is very desirable to perform event detection and discrimination at the sensor site. This can effectively increase the bandwidth of the transmission link and can reduce the overhead of the external signal processing units. Since most of the data in this form can be transmitted digitally, the external transmission protocol can be designed around a bus-organized system thus greatly increasing the data transfer speed and improving the overall signal-to-noise ratio. It is believed that for many of future closed-loop prosthetic
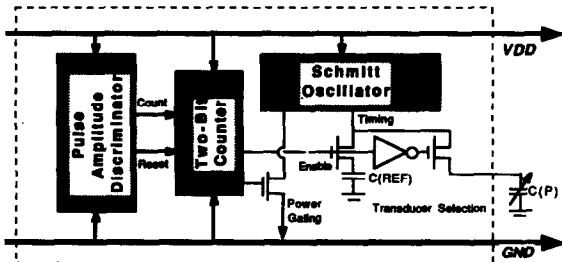
Fig. 5. Block diagram of the interface circuit chip for a capacitive pressure sensor for a cardiovascular catheter.

Fig. 6. Block diagram of the on-chip circuitry for first generation of active multichannel recording electrodes.

systems such signal processing has to be performed at each sensor site.

The techniques described above have been used in a number of integrated sensors currently under development by our group. Figure 5 shows the interface circuit designed for the capacitive pressure sensor designed for the cardiovascular catheter described above [4]. A Schmitt oscillator is chosen to detect the capacitance change. A pulse amplitude discriminator detects address and clock signals that are superimposed on the supply voltage line to allow selection of one particular site and sensor on the catheter. The output pressure data from the sensor are extracted by detecting the frequency of current variations over the power lines. This design for the interface circuit requires only two output leads and is very simple. Figure 6 shows the block diagram of the on-chip circuitry for the first generation of active multichannel intracortical recording electrodes [3]. This first generation (PIA-1) design uses per-channel amplification to enhance signal-to-noise ratio and multiplexes analog data from ten recording electrodes onto a single data lead. The circuitry requires only three output leads for data, power and ground, and can perform self-testing. The second
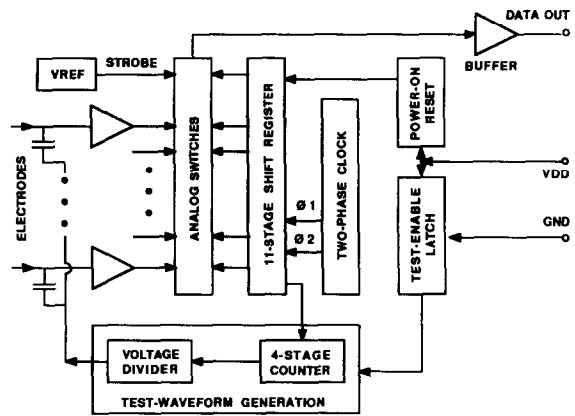
generation of these electrodes (PIA-2) is being developed [6] and utilizes a bi-directional data lead to receive analog data from the electrodes and to deliver digital data for programming and for selecting 8-of-32 recording electrodes. Three output leads are used for this design.

We are also developing a multichannel stimulating electrode which supports 16 electrodes [7, 8]. The on-chip circuitry receives power, addressing and control signals on five external leads and delivers current pulses (0 to $\pm 256 \pm 2\,\mu\text{A}$) to individual channels. The circuitry in this application is very important since it reduces the number of leads from 16 to 5. Table 1 summarizes the output lead designations and functions for these different interface circuits. It is observed that in order to reduce the number of leads, each available lead is used for multiple functions. Achieving such levels of functionality would not have been possible without extensive use of circuitry, either on-chip or in module, at the sensor site.

TABLE 1. Output lead functions and designation for five implantable biomedical transducers being developed at the University of Michigan

Sensor	Most critical function	Power	Data	Clock
Miniature pressure sensor Leads: two	Lead reduction	VDD/reset control data	None	None
Rec. electrodes, PIA-1 Leads: three	Lead reduction Amplification, buffering	VDD/reset Self-testing	Analog data Synchronization	On-chip
Rec. electrodes, PIA-2 Leads: three	Lead reduction Amplification, buffering Increased functionality	VDD/reset Self-testing	Analog output Digital input Load clock Synchronization	On-chip
Rec. electrodes, PIA-3 Leads: ??	Data reduction (perhaps telemetry)	Telemetry??		
Stim. electrodes, STIM-1 Leads: five	Lead reduction	VDD & VSS/reset Safety check	Digital in calibration Impedance testing Failure detection	Clock synchronization

Packaging and Encapsulation

Encapsulation and packaging of integrated sensors for long-term implantation in the body is of paramount importance as most of these sensors will fail due to their violation by the biological fluids. Any sensor package should not only protect the sensor and its associated circuitry from the body fluids, it should also allow for contact between the sensing site and the tissue. The requirement for this selective packaging has posed many challenges for implantable sensors. In addition, all packaging and encapsulating materials should be biocompatible. Hermetic as well as non-hermetic techniques have been and are being developed for encapsulating a variety of these sensors. Organic and thin films such as LPCVD silicon nitride and silicon dioxide, diamond films, and inorganic thin-film polymers such as polyimides and Parylene C have been used to encapsulate both sensors and electronics [9]. These materials have been used to provide adequate protection for integrated circuitry and for the implanted sensor for periods of a few months [9, 10]. Hermetic packaging using silicon–glass electrostatic bonding and silicon–silicon bonding is becoming more feasible as these technologies mature and as new techniques for low-temperature bonding of glass to silicon are being developed [11]. Encapsulation and packaging of external leads is also critical as these external connections are often the source of failure long before the sensor package itself fails.

One of the most important questions and concerns for many implantable integrated sensors is transmission of power and data/control signals to/from the outside world. Many present systems physically connect the power source through wires to the implanted sensor and extract the recorded data in a similar fashion. Although this technique is adequate for many short-term applications, for chronically implanted sensors other methods that do not involve the physical violation of the skin by output leads is desirable and often required. Telemetry of power and data using radio-frequency waves is quite attractive as it eliminates the need for wires, has basically unlimited lifetime, and is adequate for many applications. With increasing progress made in IC technologies and micromachining techniques, it is becoming possible to reduce the sizes of the receiving and transmitting antennae that are more compatible with the overall size of the integrated sensor itself [12, 13].

Conclusions

Research on solid-state integrated sensors has made rapid progress over the past decade as new technologies for silicon micromachining and microstructure fabrication, new integrated circuit techniques and fabrication technologies, and new packaging and encapsulation methods have been developed. The need for small size, reliable, high-

TABLE 2. Results and technologies derived from biomedical-related sensor research at the University of Michigan

	Multichannel intracortical recording project
Microstructures:	Modeling/characterization of boron etch-stops
	Study of fundamental scaling limits of deep boron diffusion
	Study/characterization of intrinsic stress of CVD thin films
Circuits:	Novel sensor/circuit fabrication technologies
	Study of fundamental performance limits of MOS devices
	Analysis of technology, economic, and performance trade-offs for integrated sensors and their cost-effective production
Packaging:	Nonhermetic packaging using organic/inorganic thin films
	Miniature glass/silicon packages for hermetic packaging
	Flexible ribbon cables for power/signal transfer
	Miniature pressure sensor for a cardiovascular catheter
Microstructures:	Development of a single-sided, high-yield dissolved wafer process now used in tactile imagers, flowmeters, ultrasensitive pressure sensors, two-dimensional resonant structures, and future 3-D MEMS
	Study of fundamental scaling limits of pressure sensors
	Study of sensitivity of thin-film diaphragms and effect of intrinsic stress
	Multichannel thin-film stimulating microprobes
Microstructures:	Electrical and electrochemical analysis of new stimulating thin films (IrOx used as pH and gas sensors and optical displays)
	Fundamental studies of strength and fracture of silicon microstructures

performance sensors for many biomedical applications has forced intense research, the results of which have benefited application areas beyond those related to health care and biology. Table 2 enumerates some of the technologies and techniques developed as a result of research efforts on biomedical sensors at the Univeristy of Michigan. These technologies are applied to other sensors and the biomedical sensor research programs complement, in a very real sense, our other research efforts. It is believed that this same relationship exists in many other academic and industrial laboratories and commerical sensor manufacturers.

Integrated sensors that have to operate in an environment as harsh as the body, facing some of the most challenging requirements of any sensor, and the progress made in this field will only advance the technologies required for many other sensor fields. Research and development on biomedical sensors and actuators will continue to play an important role in these regards.

Acknowledgements

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