Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 1741–1745, March 1989
Applied Physical Sciences

Optical imaging of the spatial distribution of β-particles emerging from surfaces

(autoradiography/gaseous detectors)

G. CHARPAK, W. DOMINIK, AND N. ZAGANIDIS

EP Division, European Organization for Nuclear Research, 1211 Geneva 23, Switzerland

Contributed by G. Charpak, November 29, 1988

ABSTRACT **The multiplication in gases of ionization electrons, by the effect of the electric fields between parallel electrodes, leads to the emission of light from the molecules excited in the avalanche process. The optical imaging of this light, with intensifiers, on charge-coupled devices permits the localization, in the gaseous volume, of the entrance points of the β-particles emitted by radioactive compounds placed close to or at the cathode electrode. Thin slices of anatomical samples labeled with ^{3}H show detailed structures 30 μm in size. Gels carrying ^{32}P or ^{35}S are imaged with accuracies of the order of 0.5 mm (full width at half maximum). In comparison with photographic emulsion, the gain in time for data taking is close to a factor of 100, with the advantage of linearity and wider dynamic range in the intensity measurement and a greatly improved signal-to-noise ratio.**

Many fields of research use chemicals labeled with electron-emitting radioactive elements. An important step in the measurement is often to determine the intensity distribution of the radioactive compounds localized at various spots on a surface. Photographic emulsion apposed to the surface is the most common technique for the imaging of radioactive elements because of its simplicity, low cost, and excellent spatial resolution. However, several drawbacks hamper this method: the low sensitivity leads sometimes to exposure times of several months; the nonlinearity of the response and saturation effects make it difficult to obtain accurate quantitative measurements of intensities. This has led to various attempts to find a replacement for photographic emulsions.

Multiwire proportional chambers, routinely used in high-energy physics, have been exploited for the detection and localization of electrons emitted by radioactive elements and have given birth to several commercial instruments. They rarely permit accuracies of better than 1–3 mm [full width at half maximum (FWHM)] to be reached because of two main factors: the range of β-particles in gases can be several centimeters at atmospheric pressure, and the anode wire spacing is often of the order of 2 mm for convenience in the operation of the chambers, limiting the accuracy to this value.

Gaseous detectors with a different electrode structure (1) have dealt with these two factors successfully (2). If the detecting region is limited by parallel planes of electrodes, the multiplication of electrons in the gas under the effect of an electric field is an exponential function of the distance x of the electron to the anode plane:

$$M = \exp(\alpha x),$$

where $1/\alpha$ is the mean free path for an electron drifting in the electric field to experience an ionizing collision; α is a function of the nature of the gas filling, of the electric field, and of the pressure.

Under these conditions, electrons nearest to the cathode give rise to the largest multiplication (Fig. 1). A radioactive sample emitting electrons is placed near or against the cathode plane of such a detector. Among all avalanches initiated by ionization electrons along the track of a β-particle, the one that has the highest intensity of charges is that liberated by the electron freed nearest to the entrance point of the ionizing particle. The localization of this maximum will thus, to a great extent, permit the elimination of the error introduced by the large range of the electron and the finite thickness of the detector.

An anode plane can be free of the limitations connected with the anode wire spacing of multiwire chambers and can be made of a continuous conducting surface or of a metallic mesh with very small wire spacing. There exist several electronic methods that permit the localization of the maximum of the charge collected at the anode plane.

The maximum gain M achieved under conditions of proportional amplification in a single gap can be of the order of 10^5 or even higher. It is limited by sparking produced by occasional highly ionizing events or by irregularities in the electrodes. For this reason, it is usually very impractical to work with gains larger than 10^4, which can be sufficient, in some cases, for autoradiography. For instance, with ^{3}H in a gas such as argon at atmospheric pressure, where the average β-particle of 6 keV (1 eV = 1.602×10^{-19} J) will produce about 200 initial electrons, localized within a few hundred micrometers, a gain of 10^3 is quite sufficient for each detection and localization. With radionuclides, such as ^{32}P, emitting many minimum-ionizing electrons, the number of primary ionizations in argon, for instance, is close to 30 per cm; if an accuracy of a few hundred micrometers is desirable, one has to be able to detect the signal initiated by a small number of electrons, and a larger gain may then be required.

This can easily be achieved by using a succession of gaps separated by transfer spaces, where electron swarms drift without multiplication (1). The electrodes defining the gaps are made of grids permitting the transfer of electrons from gap to gap. This considerably reduces the secondary effects due to photons or ions, which are responsible for sparking. Large gains, $M > 10^6$, are achieved, permitting the detection of single electrons produced, for instance, by vacuum ultraviolet radiation.

In the last few years, several imaging detectors based on such multistep structures have been investigated (2, 3) and accuracies of the order of 500 μm are reported for ^{32}P and ^{35}S. Similar results are obtained with a single-step multiplying gap (4).

In this work we report on a different approach to the problem of the measurement of the charge distribution of the avalanches produced by ionizing particles in a gap between

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: CCD, charge-coupled device; FWHM, full width at half maximum.

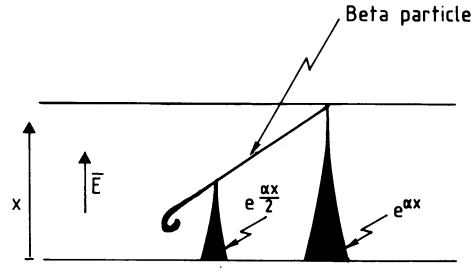

FIG. 1. Localization of the radioactive emitters with avalanches between parallel electrodes. A β-particle entering the gap produces a trail of ionization electrons in the gas filling. If the electric field E is large enough for ionizing collisions of the drifting electrons, the multiplication is an exponential function of the distance x to the anode. Determining the position of the maximum of the charge distribution at the anode gives the coordinates of the electron freed closest to the entrance point of the β-particle.

parallel electrodes. It has allowed us to obtain images of ^3H distribution in a biological sample, showing a clear picture of 30-μm anatomical details, and seems most appropriate for the information retrieval from amplifying gaps between parallel electrodes.

EXPERIMENTAL METHOD

Readout of Avalanche Position from the Light Emitted by Excited Atoms. When electrons produce ionization in gases, they also experience collisions resulting in the emission of light. The wavelengths of the emitted photons and their intensity vary over a considerable range, with the nature of the gas, the electric field, and the pressure. It has been found that with an appropriate choice of gases it is possible to obtain an emission of UV or visible photons suitable for the optical readout of the information on the charge distribution of avalanches between parallel electrodes (5). There exists some choice in the nature of the gas mixtures. In the work reported here, the results were obtained with triethylamine added to argon or xenon. The avalanches result in the emission of a broad photon line with the wavelength centered at about 280 nm and an intensity of about one photon per electron in the avalanche.

Several versions of this imaging detector have been studied. For ^3H the range of the β-particles is so small that it is impractical to have a window between the chamber and the source. The sample is made conductive by evaporating on it a thin (≈200 Å) layer of gold. The sample holder is embedded in a metallic frame, which constitutes the cathode of the amplifying gap (Fig. 2*A*).

For ^{32}P and ^{35}S, emitting electrons with a maximum energy of 1.70 MeV and 0.168 MeV, respectively, it is more convenient to have as cathode a thin window with the radioactive sample placed against it (Fig. 2*B*).

The anode is a mesh made of 50-μm interwoven wires with a pitch of 500 μm, at a distance of 5 mm from the cathode. The gases, mixed with about 2.5% of triethylamine, are flushed through the chamber at atmospheric pressure.

The volume of the chamber is limited on the anode side by a window that is transparent to the light emitted by the excited molecules. This window can be made of quartz or Aclar (polychlorotrifluoroethylene). The anode has a transparency of about 80%. Since the total lateral spread of the avalanches, 0.5 mm (FWHM), is larger than the pitch of the mesh, the images do not exhibit the structure of this mesh, and the centroid of the light distribution is apparently not affected by it, at our level of accuracy. We have studied the images obtained with single gaps, with a succession of two gaps, and also with a thin plastic scintillator converting the UV light into visible light. We will only report here on the

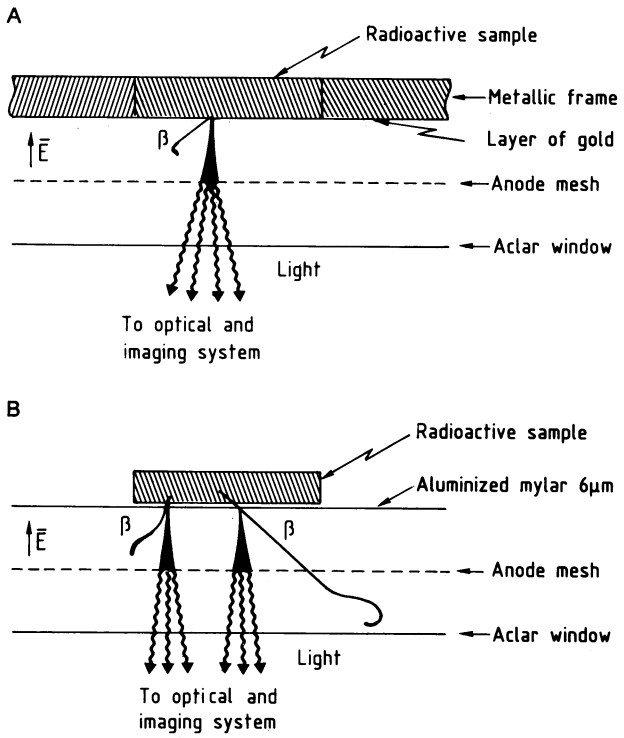

FIG. 2. Geometrical coupling of radioactive surfaces and amplifying gaps. (*A*) For ^3H the surface is covered by about 200 Å of gold and is part of the cathode. (*B*) For emitters of more penetrating β-particles, such as ^{32}P or ^{35}S, the radioactive samples are separated from the gap by a thin conductive electrode. The gas fillings in the gaps are argon or xenon, mixed with triethylamine vapors, emitting a photon spectrum centered at 280 nm. The light is transmitted through lenses to an image intensifier and CCDs read out by a computer. The avalanches produced against the anode mesh emit light, which is imaged through Aclar windows that are transparent to UV light.

results obtained with single gaps, since they display all the properties that make this approach of interest for most potential users, while the other methods introduce only a small reduction of accuracy with some practical advantages.

A reflective type of UV objective 90 mm f/1.1, placed at 50 cm from the last transparent mesh electrode of the chamber, focuses the light from the avalanches on the photocathode of an image intensifier coupled to a charge-coupled device (CCD) (Thomson 7852 CDA-80), which is a matrix of 144 × 208 pixels with a total area of 4.32 × 5.82 mm^2. Taking into account the optical parameters, each pixel of the CCD corresponds to a pixel on the surface of the sample, of 180 μm × 180 μm. The signal stored in each pixel of the CCD is transmitted to an IBM-PC/AT computer, with an accuracy of 8 bits. This is one limit to the dynamic range for a given amplification in the gas, which can be varied by changing the high voltage applied on the electrodes. With the CCD and our associated electronics, a maximum of 50 images per sec can be transferred to the computer. A photomultiplier placed close to the lens detects a light signal at every event, and the signal from it can be used for gating purposes rejecting, for instance, events producing occasional sparking, which occurs at a rate of 10 per hr.

Imaging of the Spatial Distribution of β-Particle Emitters. *Imaging of ^3H.* For every event the pixel distribution is taken into account for the calculation of the position of the electron that has initiated the avalanche. For the β-particles emitted by ^3H we have chosen xenon as a filling gas to minimize their range, estimated to be close to 100 μm for the average electrons. With the width of each avalanche being of the order of 0.5 mm (FWHM), the image covers several pixels of

the CCD. Taking the center of gravity of the light spots gives an image that displays the quality of the method. Fig. 3*A* shows the results obtained with slices, 20 μm thick, of the kidney of a rat in 40 hr, recording 2.5 events per sec. We can at present, because of the reduction of the dead time caused by the speed of the data-acquisition system, bring this time to 20 hr. Fig. 3*B* is a photograph of an autoradiogram of the adjacent slice of the kidney obtained by apposing a ^{3}H-sensitive film on it during 3 months. It displays details of the distribution of the ^{3}H-labeled compound in the collecting ducts, which are between 30 μm and 50 μm wide, but contains very little information on the relative intensities because of saturation, which is also responsible for the broadening of the image of the tubules. The image given by our detector can easily be analyzed for quantitative information, and Fig. 3*A* also shows the intensity distribution along the line crossing the image. The accuracy is obviously sufficient for observing details as small as the tubules. It is smaller than the β-particle range, since we measure the position of the centroid of the track. Fig. 3*C* shows a slice of

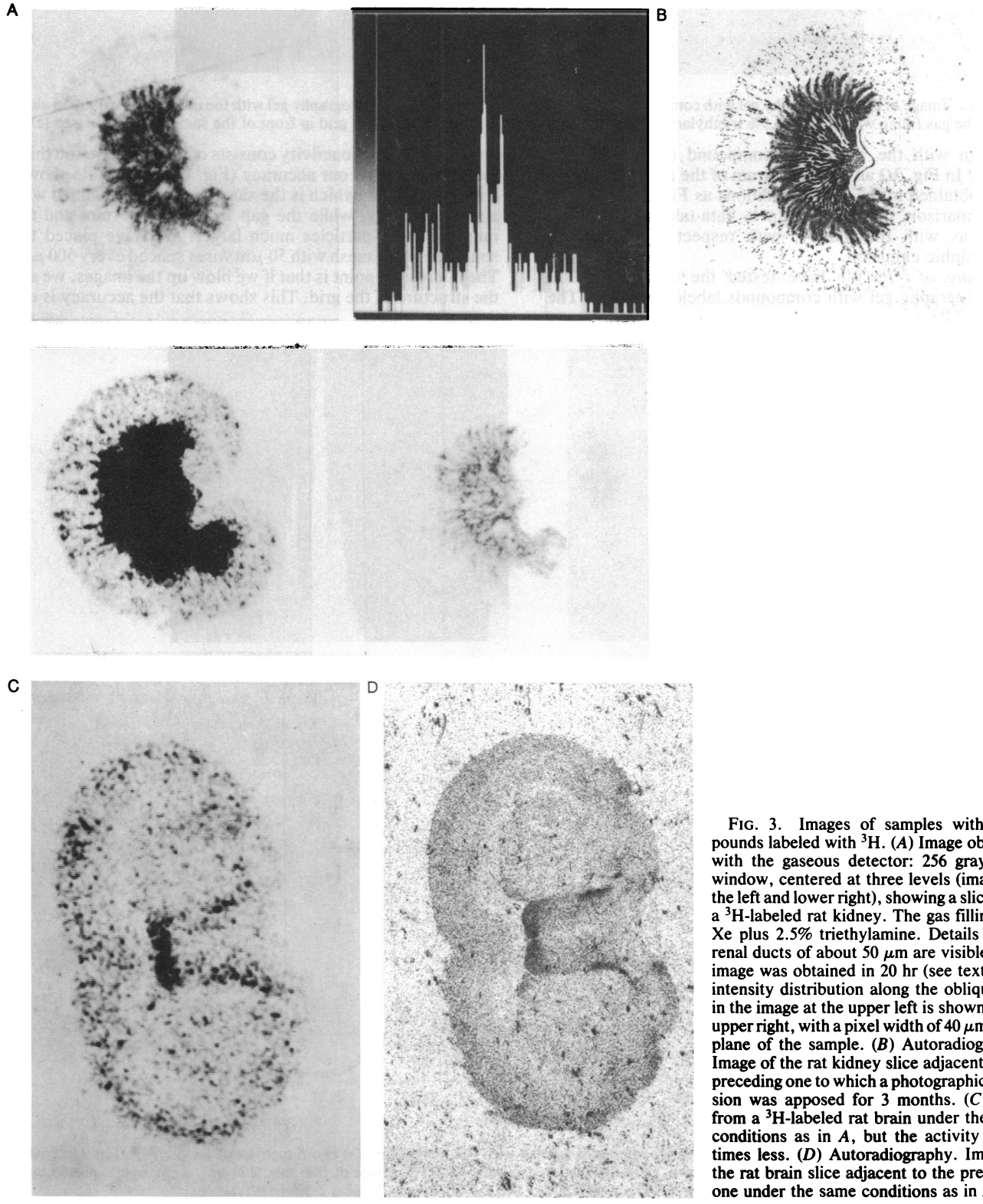

FIG. 3. Images of samples with compounds labeled with ^{3}H. (*A*) Image obtained with the gaseous detector: 256 gray level window, centered at three levels (images at the left and lower right), showing a slice from a ^{3}H-labeled rat kidney. The gas filling was Xe plus 2.5% triethylamine. Details of the renal ducts of about 50 μm are visible. This image was obtained in 20 hr (see text). The intensity distribution along the oblique line in the image at the upper left is shown at the upper right, with a pixel width of 40 μm in the plane of the sample. (*B*) Autoradiography. Image of the rat kidney slice adjacent to the preceding one to which a photographic emulsion was apposed for 3 months. (*C*) Slice from a ^{3}H-labeled rat brain under the same conditions as in *A*, but the activity was 7 times less. (*D*) Autoradiography. Image of the rat brain slice adjacent to the preceding one under the same conditions as in *B*.

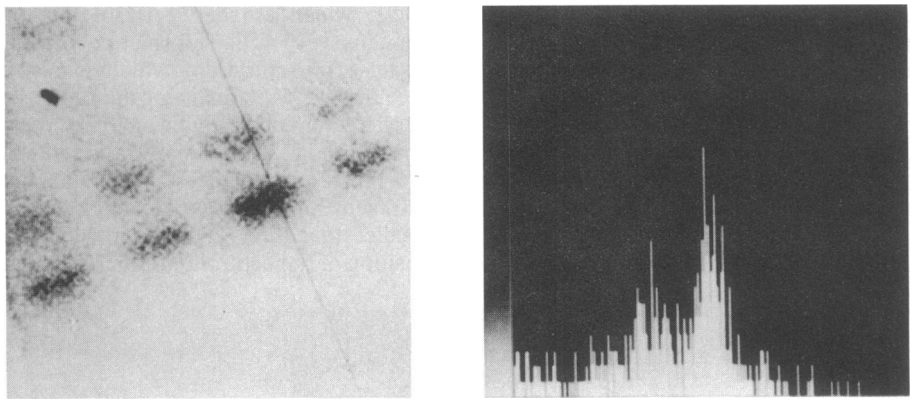

FIG. 4. Image of chromatography gel with compounds labeled with ^{32}P. Portion of a chromatography gel with the intensity distribution along a line. The gas filling was Ar plus 2.5% triethylamine; pixels were 40 μm. The structure of the grid in front of the sample is visible (see text).

rat brain with the ^{3}H-labeled compound localized at the septum. In Fig. 3*D* an autoradiogram of the adjacent slice of brain, obtained in the same conditions as Fig. 3*B*, is shown for comparison. The same gain in data-taking time is observed as with the kidney, with respect to the use of photographic emulsion.

Imaging of ^{32}P. We have tested the detector with a chromatography gel with compounds labeled with ^{32}P. The distribution of radioactivity consists of lines that are too thick to test the limit of our accuracy (Fig. 4). The results show a width of $\approx$1 mm, which is the same as the one obtained with autoradiography, while the gap thickness is 5 mm and the range of the β-particles much larger. We have placed the source behind a mesh with 50-μm wires spaced every 500 μm. The interesting point is that if we blow up the images, we see the structure of the grid. This shows that the accuracy is not

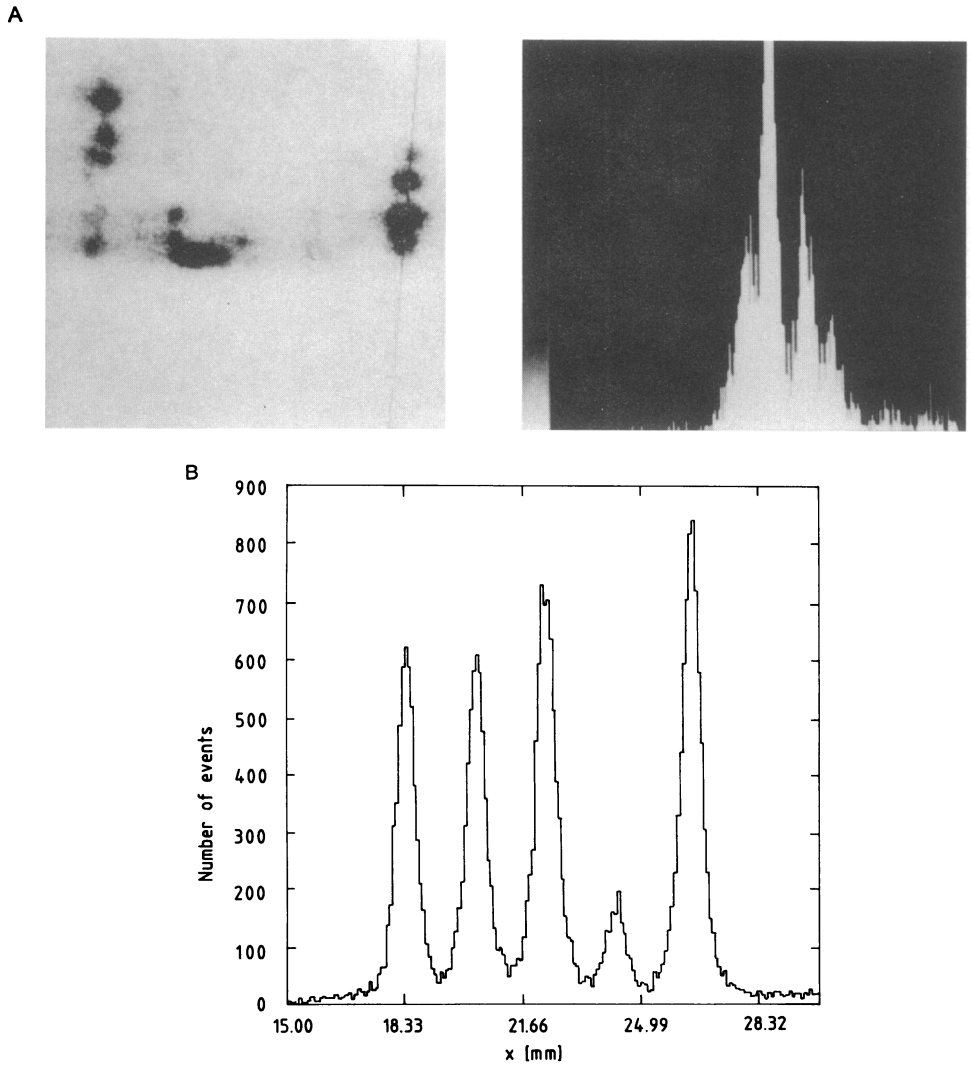

FIG. 5. (*A*) Image of an electrophoresis gel with compounds labeled with ^{35}S. A portion of a two-dimensional gel (*Left*) with the intensity distribution along the oblique line (*Right*) is shown. (*B*) Localization accuracy with ^{35}S. Image of five slits, 150 μm, 2 mm apart, placed on a non-uniform ^{35}S source is shown at a resolution of 500 μm (FWHM). The gas filling was Ar plus 2.5% triethylamine.

limited by our readout system. In cases where it is limited by the extension of the radioactive sources, it is possible to image larger surfaces by simply adjusting the optics.

Imaging of ^{35}S. For ^{35}S we used samples of a two-dimensional electrophoresis gel. We have been able to compare our results with an autoradiogram obtained in 15 days. In a period 30 times shorter, we obtained better quantitative data, as is shown in Fig. 5*A*. We have measured the positioning accuracy of ^{35}S emitters by imaging linear sources of 150-μm width, separated by a distance of 2 mm. We obtained images with a width of 500 μm (FWHM) (Fig. 5*B*).

DISCUSSION

The optical readout of avalanches in gases initiated by electrons liberated by vacuum ultraviolet Cherenkov photons or charged particles will certainly be the subject of more active research and development in high-energy physics. The discovery that adding vapors to noble gases yields a copious intensity of light (6, *) in avalanches has allowed this approach to get started. It also offers prospects of promising applications in all the domains where autoradiography techniques are used for quantitative measurement of the spatial distribution of radioactive compounds carried by biological samples or gels.

The advantage of using the emission of light instead of the electric pulses induced in avalanches stems from several factors. (*i*) A modern technique widely used in the video industry, the CCD, provides us with hundreds of thousands of pixels at low cost. (*ii*) The gaseous detectors made of parallel planes of electrodes permit, to a large extent, the elimination of the drawback of the large ranges of the β-particle in the gases. (*iii*) The research on gas mixtures emitting light of a convenient wavelength has resulted in several options permitting the photography of large surfaces on a single CCD, from great distances. Detectors with a surface of 20 × 20 cm^2, capable of imaging many small samples at the same time, are now feasible. (*iv*) The possibility of having an efficiency of 100% for every electron liberated in the gas volume and the low noise make this instrument particularly suitable for the imaging of low-intensity radioactive samples. The shape of the image of a β-particle is not circular but elliptical and depends on its range: it is almost circular for ^3H and most elongated for ^{32}P, with a peak at the beginning of the track. We have used only the barycenter of the pixels for the localization of the β-particles from ^3H. For ^{32}P and ^{35}S we have calculated the barycenter of a predetermined number of pixels close to the maximum.

*Charpak, G., International Symposium on Lepton and Photon Interactions at High Energy, 1985, Kyoto, Japan, p. 514.

We are indebted to Professors B. Roques from the Université René Descartes in Paris and J. J. Dreifuss from the Centre Médical Universitaire in Geneva for inspiring discussions on the problems of autoradiography. We thank Dr. E. Tribollet from the Centre Médical Universitaire in Geneva for her guidance in the choice of biological samples, and Dr. D. Townsend and Mr. A. Geissbühler from the Hôpital Cantonal in Geneva for their help in the image analysis.

1. Charpak, G. & Sauli, F. (1978) *Phys. Lett. B* **78,** 523–528.
2. Petersen, G., Charpak, G., Melchart, G. & Sauli, F. (1980) *Nucl. Instrum. Methods* **176,** 239–244.
3. Bateman, J. E., Stephenson, R. & Connolly, J. F. (1988) *Nucl. Instrum. Methods.* **A269,** 415–424.
4. Angelini, F., Bellazini, R., Brez, A., Massai, M. M. & Torquati, M. R. (1988) *Nucl. Instrum. Methods* **A269,** 430–435.
5. Charpak, G., Dominik, W., Fabre, J. P., Gaudaen, J., Sauli, F. & Suzuki, M. (1988) *Nucl. Instrum. Methods* **A269,** 142–148.
6. Gooch, T. K., Gilmore, R. S., Jeffery, D. R. N., Kwan, W. L., Llewellyn, T. J., McArthur, I. C., Malos, J. & Tapper, R. J. (1985) *Nucl. Instrum. Methods* **241,** 363–374.