An Eye-Opening Visit to Chi-Mei Electronics (奇美電子), an Industrial Icon of Southern Taiwan Science Park in Tainan County

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Led by Michael M. C. Lai, President of National Cheng Kung University and invited and hosted by Wen-Long Hsu, Founder, Jau-Yang Ho, President and Ching-Siang Liao chairman of the board of Chi Mei Corporation, a delegation of NCKU leaders spent the entire day at the company corporate headquarters and its massive facilities in Southern Taiwan Science Park. Members of NCKU’s delegation, besides Academician Lai, are the following:
The company, Chi-Mei, which I would like to translate as “Mysterious Beauty,” has ubiquitous business interests, ranging from chemical and food production to now an undisputed global leader in display panel production. It was founded by Mr. Wen-Long Hsu, a renaissance man of multiple talents, from being a recent violin playing partner of NCKU’s president Academician Michael Lai, to museum curator for founding one of Taiwan’s most comprehensive “free-of-charge” artistic museums on the fifth to eighth floor of its corporate headquarters (with, as expected, many Stradivarius violins) to profound and fast thinking entrepreneur.

According to Mr. Jau-Yang Ho, President of CMO (the electronics subsidiary of Chi-Mei Group,) who is also one of NCKU’s 120,000 alumni worldwide and became a recent prestigious NCKU distinguished alumni laureate, and displayed phenomenal knowledge of the company’s broad and deep information, the company is now galloping at 40% growth annually, and will soon reach $20 billion (U.S.) annual revenue in 2007/8. In addition, it will be aggressively moving into many different new but related industries, which shows the company’s understanding of the world’s market, in order to further its growth in business. Unquestionably, CMO today is not only an economic engine of Southern Taiwan, but Taiwan and Asia in general.

Although I visited Southern Taiwan Science Park (STSIPA) http://www.stsipa.gov.tw/ a few years back, this was my first visit since I assumed my position in NCKU. In the past two months I have been seeing it from afar while traveling at 180 miles an hour on the train of Taiwan High Speed Rail system. So except for getting a zipping through impression of wide boulevards and large buildings, I was not able to see much. For sure, until this visit, I did not have an in-depth understanding and impression of the scale of the operations of STSIPA.

Today, NCKU’s delegation was given a panorama view, inside and outside.

I am very happy to notice immediately that our “tour guide” was none other then our distinguished alumnus, President Ho himself, who stayed with us throughout the day. We first went to one of the gigantic CMO buildings in STSIPA, where Mr. Ho gave us a tour of the display room, followed by an in-depth presentation of CM group in general and CMO in particular. It was from this presentation I began to realize the scale and depth of the company.

Let me say a few words about the company’s manufacturing clean room facility. The one we visited is the so-called 6th generation panel display facility. It can house, I was told, some six football fields in area, and it has some 4 floors (thus 24 football fields in total!). I should mention that there are many equally large, if not bigger facilities in the park, along with many other companies.

Entering the clean room facility, which mostly is class-1000, with scattered areas of class 10 (and even class 1) require delegation members to “suit-up.” I always thought that from seeing from afar that suiting up in this manner would be suffocating, but this experience told me that it was really quite pleasant, although I have to admit that walking around for at least “several miles” inside the facility made me sweat quite a bit.

The manufacturing facility we visited is entirely computer controlled, and all motions were carried out by

**ARTICLES**

**COMMENTARY**

- Da Hsuan Feng, Senior Executive Vice President
- Tommy Tzeng, Vice President for Research and Development
- Y. H. Chang, Dean of Management
- Andy Fuh, Dean of Science
- Wen-Teng Wu, Dean of Engineering
- Jen-Sue Chen, Chair of Materials Science and Engineering
- Wei-Chou Hsu, Chair of Electrical Engineering
- Jiin-Yuh Jang, Chair of Mechanical Engineering
- Yan-Ten Lu, Chair of Physics
- Hung-Shan Weng, Professor of Chemical Engineering and Former President

The day began at 8:30 am in the morning of November 23 and ended at 4:00 pm. At the end of the visit, I can detect that all delegation members were intellectually and physically drained! I will explain why!

Something about CMO

In the past several decades, Chi-Mei Corporation is rapidly rising as one of the most powerful global corporations in Asia Pacific Basin. Its corporate headquarters is in Tainan, Taiwan, which is about half an hour by car from National Cheng Kung University through the winding roads of ancient Tainan.
robots. When asked whether the facility is runned at 24x7, Mr. Ho suddenly turned into an enthusiastic entrepreneur and replied that

“not only should it be 24x7, but we measured by how many seconds we lost if ever the facility stops function. We measured our production, thus money making process, with production in number of seconds in time. In fact, if power goes down, the power supplier needs to compensate us because that means significant monitory, hence profit, loss!”

With such emphatic determination, it is no wonder that Chi-Mei is now the world leader in panel display production.

There is no question that each science park in the world needs an ICON. In Silicon Valley, HP and CISCO assume this role. In Seattle, it is Microsoft. In Hsinchu’s Science Park in northern Taiwan, it is Taiwan Semiconductor Manufacturing Corporation, or TSMC.

Looking at the vast areas and rapid growth of STSCPA, if not already, Chi-Mei is rapidly assuming the ICON status!

Lunch and discussion with CMO leaders

Lunch was held in Tainan’s city corporate headquarters, with the two leaders Mr. Hsu and Academician Lai, greeting each other as old friends. As I mentioned earlier, these two individuals became “violin partners” ever since Lai assumed the presidency of NCKU. Both, with deep interest in music, believed intuitively that education is far more important than “training.”

Discussions between the two groups, NCKU and CMO leaders could be summarized as follows (according to me, since no one took notes and so I did this through memory. Hence mistakes are mine!)

- All agreed that CMO and NCKU have a special relation, which was developed in the last four decades. Indeed, even Mr. Hsu himself, who did not study in NCKU, was closely linked with the university for the past decades. All agreed that with the new leadership of President Lai, the timing is perfect for this collaboration.
- It is interesting that in any region, having only industries without powerful university or universities is like a “one spouse marriage!” In Silicon Valley, besides HP and CISCO, there are Stanford and UC Berkeley. In Boston, there are defense industries (such as Raytheon) and universities (such as Harvard and MIT). In San Diego, there is bio-economy and UCSD. In Seattle, there are Microsoft and Boeing and University of Washington. So, it is interesting that Chi-Mei and NCKU are the partners of this “marriage,” especially when individuals from both organizations have such deep and intertwining relations (one of NCKU’s most distinguished professor is an independent member of the board of Chi-Mei, for example.)
- The economic and intellectual successes of the region of southern Taiwan will be driven by high quality people. High quality people will demand not only exciting professional careers, such as those provided by Chi-Mei and NCKU, they also will demand quality of life, which range from having exciting cultural activities to schools for their children. There is no question that when Chi-Mei and NCKU work synergistically and complementarily, this can and will happen.
- Mr. Ho gave the most heart warming summary of the day. He said that as far as Chi-Mei is concerned, developing a deeper and closer relation with NCKU is a “natural.” He also said that becoming a distinguished alumnus this year is one of the highlights of his life. Ever since he completed his education in NCKU nearly four decades ago, he came to work for Chi-Mei. So CMO is his first and last company. In today’s fast changing jobs landscape, this is LOYALTY! More over, in recent years, according to Mr. Ho, that it is becoming completely transparent that CMO has reached the point where developing a global reputation is no longer an option, but a must. To this end, both groups at the luncheon agreed that a
closer collaboration will allow CMO and NCKU to assume global “icon” status for our region.

- True to his high quality leadership, Mr. Ho was philosophical when he said that “opto-electronics” not only involves science and technology, it also is one area where “seeing” is critical. This is true whether one is talking about the most advanced TVs or the best display of breast cancer images. Both NCKU and Chi-Mei are now deeply involved in this area, with expertise, both in knowledge and businesses, that range from “panel display production” to biomedical photonics engineering. By seamlessly amalgamating both may and can have the effect of rendering the southern Taiwan region to become a world’s most exciting “OPTICS VALLEY!”

- A reality in Taiwan is the Government’s incommensurate support of north and south. However, during our discussion, this “wei-ji” was viewed as an incentive for boosting collaborations between academia and industry, especially those driven by intellectual innovations. Interestingly, it was noted that in order for CMO to be a world leading player in its business, it needs to invest annually 200 billion NTD (roughly $6 billion US) in physical infrastructure. Mr. Ho also mentioned that due to the extreme rapid change of panel display market, one of CMO’s most serious challenges is to find and keep large number of well educated individuals to propel the business. On the other hand, it was recognized by all around the table that only world-class universities will attract first-rate students. World class universities are built solely on human intellectual underpinnings. An example was mentioned about the 1972 recruitment of Willis Lamb, a Nobel laureate in physics from Yale University to the University of Arizona. The arrival of Lamb was followed by a significant number of truly greats. In a sense, Lamb was de facto the genesis of Tucson’s transformation to eventually becoming the world’s most robust “optics valley.” With this in mind, it seems logical that CMO could consider investing a few percent of its total investments as incentive to attract world’s best to our region. This will for sure produce a deep and profound impact on boosting the human resource quantity and quality, from students to faculty. It can have the profound impact of sowing the seed to greater prosperity for all concerned in the (near) future.

- One of the responsibilities of NCKU is thus clear. We need to become a world renowned university as rapidly as possible, so that we can attract more and more world class students, such as Mr. Ho, to feed into industries in the region. With us as the economic engine of the region, I cannot think of anything that can have more profound impact than this mission.
The applications of pens are expanding with the development of technologies. The pen-based products increased the opportunities for people to use pens to write on screens. A touch pen used for screen writing is a hand tool and can be considered as an extension of the hand. The proper design of hand tools requires technical, anatomic, anthropometric and physiological considerations. This study investigated the sizes of the touch pens in the current markets to explore the proper length and diameter of a touch pen and observed the user behaviors on the pen-based computers to find natural postures of upper limb (forearm, hand and fingers) and hand gripping. Then the hand anthropometric measurements and the design principles of hand tools were taken into consideration during the touch-pen design for increasing comfort and performance.

The concept of this study was developed from investigations, innovated design and evaluations. The investigations were to survey the sizes of touch pens in the current markets, to explore the behavior of touch-pen used on pen-based computer and to interview the user’s opinions after operations. The results of the observations demonstrated that when a user point-and-clicked on the screen, the forearm hung in the air and did not use their elbow or other hand part for support. Most users held touch pens high on the penholder with a finger grip that appeared loose; that is, the grip pattern was similar to pinching a stick and wielding it. Furthermore, based on observational results and user feedback, this study identified that the loose grip pattern sometimes allowed the pen fall or resulted in incorrect pointing-and-clicking, owing to instability of the pen. For writing task, the feature “using local support” (53.3% using local support, 46.7% not using local support). 6.7% used their wrist (including the side of the hand) for support, 10.0% used their elbow as support, and 36.7% used their little

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**Design Approach for Increasing Stability and Performance of Touch Pens in Screen Handwriting Tasks**

**Fong-Gong Wu**, **Shuyi Luo**


(SSCI) NSC93-2213-E-006-078


Taiwan Patent No.: M273460
finger for support. Moreover, the users’ fingers appeared to strenuously grip the pen and their fingers become deformed or exert excessive force during screen writing task. While drawing geometric figures on the screen, 63.3% of users did not use support and 30.0% used their little finger for support. Pen holding gestures vary while drawing. Some people use three digits, four digits, or even five digits to hold a pen, whereas others use their little finger for support.

To further understand why people did not write and draw with the forearm supported on a screen, but use their little finger, wrist or elbow for support. This study also collected user opinions by interview. The interview results were as follows:

- The cause of unnatural gestures was that users could not maintain a straight wrist. For instance, most people write with their wrist resting against the screen or screen edge. While performing tasks, most users had excessive dorsiflexion. When a user’s elbow rested on a table, their hand appeared to have excessive palmar flexion. When the little finger rests against the screen, the finger can easily drift into excessive extension.

- When writing on paper, people write with their forearm supported on a table or other surface. However, why do users typically use their wrist, elbow or little finger for support when writing on a screen? Interview results indicated that the use of the little finger for support was a habit carried over from past computer use, resulting from user’s fear of scratching or staining the screen. Furthermore, using the wrist, elbow and little finger as local support can also provide considerable stability and facilitate substantial dexterity while writing on a screen.

In terms of ergonomic design, a neutral hand posture is one in which the hand is straight, rather than bent up, down, sideways or twisted. Observational results clearly demonstrated that the key design goal for a touch pen form screenwriting was to eliminate unnatural postures, and increase operational stability and performance.

Before the innovated design, this study firstly examines the size effects on the performance of various touchpens in the current markets. Three different lengths (80, 110 and 140mm) and four different diameters (5.5, 8, 11 and 15mm) were tested in three screen tasks for determining the ideal dimensions of the pen-based products. The sizes of 140mm x 8mm were suitable for three tasks using. Following, the innovated design of touch pen was created depending on the results of the proper sizes, behavior observations, as well as the theories of hand motion and design principles. Several studies proposed several methods for increasing hand stability. Handle should be designed to have large content surface to distribute the force and to direct it to less-sensitive areas, such as the tough tissues between the muscles of flexor pollicis brevis and adductor pollicis, and stretches across the thumb cleft. This novel pen is called the five-point grip pen (FPGP).

To further understand the usability of the FPGP, the final stage was design evaluations. In the first place, to understand whether the FPGP is superior to the normal touch pen on performance and upper limb postures. The performing times and error rates were the dependent variables. The upper limb postures and the grip patterns were surveyed and evaluated. The experimental and observational results showed: (1) the performance of the FPGP is superior (with fewer error rates) than the common touch pen in three screen tasks. (2) Although the touch pens with or without a brace did not differ in terms of time performance, fewer errors occurred in the writing and pointing-and-clicking tasks when a touch pen with a brace was used. This study recommends that tasks required high degree of accuracy, a touch-pen with a brace should be helpful. When drawing on a screen people can use the FPGP to improve hand stability and save time. (3) The advantages of the FPGP include: increased hand stability, improved unnatural postures, and provided adjustability. The disadvantages of the FPGP were the observational results and arrived at the idea of adding an extra contact point under the tough tissues of the thumb cleft to diminish the need of using wrist, little finger and elbow for local support while operating a touch pen. The tripod grip, the most common gripping method, uses four contact points: thumb; index finger; middle finger; and, an additional point made by the thumb cleft. In addition to the fourth contact point, a fifth contact point was added to the proposed pen below the thumb cleft to minimize unnatural gestures and slipping. The position of fifth point is located on the tough tissues of the thumb between the muscles of flexor pollicis brevis and adductor pollicis, and stretches across the thumb cleft. This novel pen is called the five-point grip pen (FPGP).
The concise design processes of the Five Point Grip Pen (FPGP)
Active matrix organic light-emitting (AMOLED) are considered potential future display technology, as they are thin, have a high degree of brightness, are self-emitting, have fast response time, a high contrast ratio and are flexible. The approaches for driving AMOLED pixel circuits can be divided into two kinds: the current programming method, and the voltage programming method.

(1) Current Programming Method
The current programming method can be divided into current copy and current mirror. Current copy technology adjusts the control-signal and pixel structure to store sufficient voltage in the capacitor to generate the same input data current (IDATA). Then, TFT switching is controlled and the IDATA is copied and functions as the OLED current. Conversely, the current mirror technology with a symmetrical structure produces the driving current, which is multiple IDATA. The current method can overcome variations in electrical characteristics of the TFT process, such as mobility and threshold voltage. However, these current-programmed methods require prolonged settling time at a low data current and inconvenient constant current sources that control submicrometer ampere-level current in peripheral drivers. Thus, the current driving method is unsuitable for large-high-resolution displays.

(2) Voltage Programming Method
The compensation principle of the voltage driving method can be sorted as self-compensation and TFT-matching. The self-compensation method stores the threshold voltage (VTH) information of driving TFT for compensation during the programming process. The TFT-matching method compensates for threshold voltage variations when driving TFTs by utilizing the neighboring TFT VTH, which is assumed to have the same electrical characteristics as the driving TFT. Additionally, the voltage driving method is appropriate with fast programming time for application to large-high-resolution displays. Table 1 compares current and voltage program methods.

This proposed circuit by low-temperature poly-silicon (LTPS) or amorphous silicon (a-Si) techniques, presents a novel simple driving scheme using three n-type TFTs for AMOLEDs. Compared with existing current programming and voltage programming circuits, the proposed pixel circuit does not require time of VTH generation; thus, the control signal is as simple as that of the conventional 2T1C pixel circuit. Furthermore, the proposed circuit reduces the number of components in a pixel, thereby improving the aperture ratio. The proposed circuit easily satisfies the refresh time requirement in large-high-resolution OLED.

Table 1: Comparison between voltage programming and current programming methods.

<table>
<thead>
<tr>
<th>Method</th>
<th>$V_{TH}$ Compensation</th>
<th>Charge time (low gray level)</th>
<th>Signal Source Manufacture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage Programming</td>
<td>Provide</td>
<td>Fast</td>
<td>Easy</td>
</tr>
<tr>
<td>Current Programming</td>
<td>Provide</td>
<td>Slow</td>
<td>Difficult</td>
</tr>
</tbody>
</table>

A conventional pixel circuit, composed of two TFTs and one capacitor, suffers from a non-negligible VTH variation results in display non-uniformity. Some studies used more than 4 TFTs to compensate for VTH variation. An excessive number of TFTs results in complex control lines that decrease the aperture ratio and luminance of displays. Therefore, how to best simplify the pixel circuit is an important issue.

Figure 1 depicts the equivalent 3-TFT pixel circuit, its controlling signals, and the layout of the proposed circuit. For signal lines, the proposed circuit merely requires a data line and scan line, requirements similar to those of 2T1C conventional pixel circuits. The pixel circuit operates in programming mode and emission mode (Fig. 2). The operational principle is described as follows.
**1) Programming mode:**
Figure 2(a) shows the programming mode, the select line (VSEL) goes to high voltage such that TFT3 is turned on and the data voltage VDATA is stored in the storage capacitor Cs through TFT3.

\[
l_{\text{data}} = \frac{1}{2} l_{\text{bias}}(V_{\text{gs},\text{R}1} - V_{\text{gs},\text{R}2})^3
\]

\[
l_{\text{bias}} = \frac{1}{2} l_{\text{bias}}(V_{\text{gs},\text{R}1} - V_{\text{gs},\text{R}2})^3
\]

\[
\Delta V_{\text{TH,FAB}} = \Delta V_{\text{TH,T2}} - \Delta V_{\text{TH,T1}}
\]

**2) Emission mode:**
In the emission mode, showed in Fig. 2(b), VSEL goes to low voltage such that TFT3 is turned off. The driving current passing through the OLED is determined based on the difference between the drain current of TFT1 (ID1) and the drain current of TFT2 (IBIAS). In this circuit, VBIAS must be selected properly to ensure that for the entire VDATA range, TFT3 remains in the saturation region, thereby satisfying the following condition:

\[
\text{VBIAS} \leq \sqrt{A \cdot V_{\text{ML,T2}}}
\]

where \(V_{\text{TH,T2}}\) denotes the threshold voltage of TFT2 and only when the gate-source voltage of TFT2 is larger than \(V_{\text{TH,T2}}\); TFT2 remains in the saturation region because TFT2 is a diode connection. The OLED current is determined by ID1 and IBIAS as follows:

\[
\frac{dI_{\text{OUT}}}{dV_{\text{OUT}}} = -k_{\text{f1}}(V_{\text{gs},\text{R}1} - V_{\text{gs},\text{R}2}) + k_{\text{f2}}(V_{\text{gs},\text{R}1} - V_{\text{gs},\text{R}2})
\]

To elucidate how the VTH shift of TFT1 and TFT2 affects the OLED driving current in the proposed circuit, Automatic Integrated Circuit Modeling Spice simulation (AIM-SPICE) is performed. Notably, VDD is supply power line, and VSS is common ground. Simulation model parameters were based on the measurement of the fabricated OLED and poly-Si TFTs.

The OLED current is based on the difference between ID1 + ΔID1 and IBIAS + ΔIBIAS, where ΔID1 and ΔIBIAS are current variations due to the threshold voltage variations (ΔVTH = −0.33 and + 0.33 V) of TFT1 and TFT2, respectively. Figure 3 presents that ΔI1 is approximately equal to ΔIBIAS at different input VDATA and VTH shifts, and consequently, the output OLED device has similar I–V characteristics despite the variation in poly-Si TFT characteristics.

The plot shows a successful compensation for OLED current and also indicates that the OLED output current is independent of VTH variation with different input data signals. To be more specific, when the input data voltage ranges 2–8 V, the error rates in the proposed pixel circuit are all < 1.5%. Therefore, the OLED current in novel pixel circuit exhibits better immunity against the VTH variation of poly-Si TFTs.

Fig. 5 presents the nonuniform output current of an OLED simulated with combined VTH variation of poly-Si TFT during programming. The traditional 2T1C input data voltage is normalized to compare the nonuniformity of OLED current with that of the proposed circuit using the same OLED current. Compared with
the nonuniformity of a conventional 2T1C pixel circuit (>25%), the nonuniformity of the proposed pixel circuit is significantly reduced (<2%).

The assumption in the proposed pixel circuit is that the electrical characteristics of TFT1 and TFT2 are ideally the same. If the threshold voltage of neighboring TFTs ($\Delta V_{TH\_DIFF}$) varies by 0.08 V, the proposed pixel circuit tolerates 0.08-V threshold voltage variations between TFT1 and TFT2 with an output current error rate of < 5%.

Substituting $\Delta V_{TH\_DIFF} = V_{TH\_1} - V_{TH\_2}$ into (2), the following equation is obtained:

$$\frac{dV_{OUT}}{dV_{TH}} = k_1(\frac{1}{g_{m1}} - \frac{1}{g_{m2}}) + k_2(\frac{1}{(V_{TH\_1} - V_{TH\_DIFF})} - \frac{1}{(V_{TH\_2} - V_{TH\_DIFF})})$$

(4)

Just after the panel is fabricated, although $|\Delta V_{TH\_DIFF}|$ exceeds 0.08 V, VBIAS can still be adjusted to make $g_{m1} = g_{m2}$. The worst case of $\Delta V_{TH\_DIFF}$ is set to 0.3 V; thus, $\Delta V_{TH\_DIFF}$ varies from -0.3 to 0.3 V as $\Delta V_{BIAS}$ is adjusted from -2.7 to -3.3 V. Therefore, the proposed pixel circuit provides stable OLED current. However, when the VBIAS line is already set in the panel and after extended operation with VTH varied, the VBIAS line is difficult to adjust.

Whether using the current or voltage driving method, existing compensating pixel circuits have complex pixel structures. Furthermore, fast scan time and high aperture ratio are essential for large-high-resolution displays. The proposed approach, composed of three n-type TFTs and one capacitor, does not need time for VTH generation such that the control signal waveform is as simple as that of a conventional 2T1C pixel circuit and is significantly easier to manufacture. Furthermore, the proposed pixel circuit has been issued a Taiwanese patent.
Optical sensing approach generally involves some form of fluorescence/radioactive labeling. This additional step not only increases the time and cost of the procedure, but also increases its complexity and potentially interferes with the molecular interaction by occluding binding sites or inducing conformational changes of the samples, hence leading to false negatives. Therefore, various label-free methodologies have been presented to perform biomolecular interaction analysis (BIA). Surface plasmons (SPs) are oscillations of the free electrons located on the surface of metals. When the phase velocity of an incident evanescent transverse magnetic (TM) light wave matches that of the SPs, the so-called surface plasmon resonance (SPR) phenomenon occurs, and virtually all of the incident photon energy is transferred to the SPs. SPR biosensors based on the Kretschmann configuration, which uses the attenuation total reflection (ATR) prism coupler method to excite the SPs, provide a better detection limit than other conventional methods. However, the Kretschmann configuration has a number of drawbacks, including the need for a highly sophisticated and precise metrology system and the requirement for a matching-index oil to couple the incident light from the prism into the metal surface on which the biomolecular interactions take place. Therefore, a coupled waveguide-surface plasmon resonance (CWSPR) biosensor developed in this study provides a highly sensitive and accurate detection performance. Furthermore, its simple optical setup enables the kinetics of biomolecular interactions on the sensing surface to be analyzed on an on-line basis without the need for prism coupling compared to that of a CWSPR device based on the Kretschmann configuration.

incident TM mode white light as its propagation constant, $k_{\lambda}^d$, is near zero and lower than that of SPs, $k_{sp}$:

$$k_{\lambda}^d = \frac{2\pi}{\lambda} \left[ \frac{1}{\varepsilon_x} \sin \theta + \varepsilon_x(x) \right] \approx \frac{2\pi}{\lambda} \sqrt{\varepsilon_x}$$

where $\lambda$ is the wavelength of the incident light and $\theta$ the incidence angle is zero for a normally incident light. However, the propagation constant of the incident light parallel to the grating surface is altered as follows:

$$k_{\lambda}^d = \frac{2\pi}{\lambda} \left[ \frac{1}{\varepsilon_x} \sin \theta + m \cdot \frac{2\pi}{\Lambda} \right]$$

where $m$ is the diffraction order and $\Lambda$ is the diffraction grating period. As follows from Eq. (2), the new propagation constant of the normally incident white light ($\theta = 0$) with a subwavelength grating at $m = 1$ can be enhanced to match the real part of the propagation constant of SPs as Eq. (1) at a specific wavelength. In analyzing subwavelength diffraction gratings, researchers have generally employed rigorous diffraction theory (rigorous coupled wave analysis, RCWA) or effective medium theory. In RCWA, the electric field in the periodic structure is expanded as the linear combination of...
the spatial harmonics. Meanwhile, in the modal method, the electric field in the diffraction grating is expanded as the combination of the modes which individually satisfy the waveguide wave equation and are permitted to be expanded by the infinite spatial harmonics.

Fig. 1 presents a schematic illustration of the current CWSPR biosensor with a subwavelength grating structure. Fig. 2 compares the reflectivity spectrum of the proposed CWSPR biosensor with that of a biosensor with a similar configuration but with no waveguide layer. Fabrication of the current biosensor commenced by spinning a resist layer of polymethyl methacrylate (PMMA, MicroChem Corp.) onto a Pyrex plate of thickness 1 mm. A uni-dimensional diffraction grating measuring 100 100 μm² was then patterned using a scanning electron microscope (SEM) equipped with a lithography system. The pattern was developed using a solution of isopropyl alcohol (IPA, Merck) and iso-butyl methyl ketone (MIBK, Merck). Subsequently, a layer of nickel was evaporated and then lifted off to create an etching mask. An anisotropic reactive ion etching process using a fluorine ion base was used to etch a subwavelength grating with a depth of 35 nm. The nickel mask was removed and a radio frequency sputtering process was used to deposit a Ta2O5 waveguide layer of thickness 285 nm and then a gold film of thickness 40 nm. The following reagents were used in the current experiments: carboxyl-terminated 16-Mercaptotetradecanoic acid (MHDA, Aldrich), N-Ethyl-N-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC hydrochloride, C8H17N3•HCl, M.W. = 191.70 g/mole, Fluka), N-Hydroxysuccinimide (NHS, C4H5NO3, Mw = 115.09 g/mole, Sigma), 0.5 μM protein G (from Strep-tococcus Sp., Mw = 22,600 g/mole, Sigma) dissolved into a 10 mM Tris-HCl buffer solution (pH 7.6, and 150 mM NaCl), and 1.0 μM anti-albumin antibody (from goat, Sigma). The surface was rinsed in deionized water, cleaned with ethanol, and dried in pure nitrogen gas. The biochip was then soaked in a 1 mM MHDA ethanol solution for 6 hours. After being soaked, the biochip was once again rinsed, cleaned and dried using deionized water, ethanol, and nitrogen, respectively, and then soaked in a 2 mM EDC 5 mM NHS solution for 12 h.

Fig. 4. Dynamic response of CWSPR during antibody interaction with protein on sensing surface. Fig. 3. Schematic illustration of normal incident spectroscope.
In the current optical metrology system, a white light emitted from a single mode optical fiber is collimated into the microscope objective lens ($4\times$, NA = 0.1) and focused on the sensing surface with a spot size of less than 100 $\mu$m. (See Fig. 3.) During the current molecular interaction detection processes, the specimens were pumped at a constant flow rate of 85 $\mu$l/min into a reaction cell maintained at a temperature of 27±0.1 °C. For biomolecular immobilization on the gold sensing surface, the 1 mM MHDA ethanol solution was immobilized on the gold film to form a self-assembled monolayer of the corresponding thiolate (after approximately 6 h). The biosensor was then soaked in the 2 mM EDC 5 mM NHS solution for 12 hours. Fig. 4 illustrates the variation of the resonance wavelength over the course of the dynamic response process of the thiol-modified sensor. After 212 minutes, Tris-HCl buffer was injected to wash away the nonspecific bindings, causing the resonance wavelength shift to fall to 5.7 nm. Although the optical measurement system and the proposed device are quite sound, we found some problems in the practical use. To excite SPs in a metallic film via subwavelength grating enhancement, it is preferable to use highly collimated white light as a continuum of in-plane wave vectors. However, a highly collimated white light is hard to be narrowed down to the very small sensing area (0.1×0.1 mm2) by the SEM lithography system. Therefore, the incident white beam contains many wave vectors that will excite secondary and tertiary SPs. This leads to the reflectivity spectrum broadened to decrease the measurement resolution. In addition, to develop the subwavelength grating structure is with an expensive lithography process. However, as designs are finalized, ordinary semiconductor manufacturing or new nanoimprinting techniques will be employed allowing extremely low cost devices to be fabricated.

In the summary, the CWSPR biosensor with a subwavelength grating structure proposed in this study provides a feasible and straightforward optical sensing platform for performing biomolecular interaction analysis in real time. The optical metrology system proposed in this study is more straightforward than the Kretschmann ATR configuration and is less sensitive to slight variations in the angle of the incident light.
Density estimation is an important and challenging problem. It can be applied to many other areas such as discriminant analysis, image processing, projection pursuit, and bump hunting, while in high-energy physics bumps in the underlying density of the observed data gives evidence concerning elementary particles, see Good and Gaskins [Journal of American Statistical Association (1980), 75, 42-73] for more details.

Let $X$ be an $n \times d$ ($d \geq 1$) data matrix of random vectors $x=(x_1,\ldots,x_d)$, where $x_1,\ldots,x_d$ are independent observations drawn from a $d$-dimensional density $f(x)$. Let $x_{ij}$ denote the $ij$-th entry of $X$. Throughout, unless otherwise specified, $\sum$, $\prod$ and $\int$ are taken over $i=1,\ldots,n$, $j=1,\ldots,d$ and $\mathbb{R}^d$, respectively. We consider the variable product kernel estimator of $f(x)$ of the form

$$\hat{f}(x) = n^{-1} \sum_{i} \prod_{j} h_j^{-1} k((x_j - x_{ij})/h_j)$$

where $k(t)$ is a univariate symmetric probability density (called kernel) and $h=(h_1,\ldots,h_d)$ is the variable bandwidth. Selecting a proper $h$ is a crucial step in estimating $f(x)$. The estimate $\hat{f}(x)$ allows the bandwidth to vary from one observation to another. It gives the flexibility of using a smaller bandwidth (hence reduce the variance of the estimate) in regions where there are relatively few observations.

A commonly used measure on the global accuracy of $\hat{f}(x)$ is the mean integrated squared error (MISE)

$$M(h) = \mathbb{E} \int (\hat{f}(x) - f(x))^2 dx.$$ 

Let us write $h=hb$ with $b=(b_1,\ldots,b_n)$. We shall call $b$ the local bandwidth factor and $h$ the global smoothing parameter. The common strategy is first choosing $b$ adaptively, and then choose $h$, by regarding $b$ as fixed and given, so that an estimate $\hat{M}(h)$ of $M(hb)$ is minimized over $h>0$.

Abramson [Annals of Statistics (1982), 10, 1217–1223] suggested the square-root law for choosing the local bandwidth factor, regardless of dimension $d$, and showed that the local bias associated with the square-root law is of higher order. Other adaptive methods that achieve a local or global bias of higher order have been studied by Sain and Scott [Journal of American Statistical Association (1996), 91, 1525–1534] and Sain [Computational Statistics & Data Analysis (2002), 39, 165–186], among others.

We propose a new method that is completely different from any of the existing methods. Our method is neither motivated by bias reduction nor derived from precise mathematical calculations. Specifically, our method (i) applies standard techniques from cluster analysis to divide the data set into clusters and then assign the local bandwidth factor $b_i$ to $x_i$ according to the average level, which reflects the average local clustering, of $x_i$ in the dendrogram (tree diagram); and (ii) uses an adaptation of the stabilized fixed-bandwidth selector of Wu and Tsai [Probability Theory & Related Fields (2004), 129, 537–558] to select the global smoothing parameter. The proposed method in selecting $b_i$ will be called the average cluster method.

The two steps in selecting $b_i$ are: (i) applying the agglomerative hierarchical clustering algorithm and, in particular, the average linkage method to cluster the $n$ observations $x_1,\ldots,x_n$ and (ii) letting $b_i$ the average distance level of $x_i$ in the dendrogram. Specifically, if $n_i$ denotes the total number of times a cluster containing $x_i$ is merged into a larger cluster (i.e., total number of mergers that involve $x_i$), and $l_1,\ldots,l_n$ the distance levels at which these $n_i$ mergers take place. Then $b_i = \frac{1}{n_i} (l_1 + \cdots + l_n)$.

Since in the above scheme clusters are formed from the individual observations by merging nearest neighbors, $b_i$ can be viewed as the average merging distance required in forming the nested sequence of clusters $\{x_i\} = C_0 \subset C_1 \subset \cdots \subset C_n = \{x_1,\ldots,x_n\}$.
Evidently, $b_i$ will be small if $n_i$ is large (i.e., a large number of mergers involve $x_i$) and the majority of the $I_i$ are small, while the former indicates that $x_i$ is in the main part and the latter indicates that $x_i$ is in a relatively dense region of the data set. This explains why this scheme should work.

For the rest, the MISE is denoted by $M(h)$, as a function of $h$, while $b$ is treated as fixed and known. We use $f(x)$ to denote the $d$-dimensional Fourier transform of any $f$, where $t=(t_1,...,t_d)$. The sample characteristic function is denoted by $\hat{\phi}(t)$. Furthermore, we denote $K(x)=\prod_{i=1}^{d}k(x_i)$, $\hat{\phi}_{K,M}(t)=e^{-\frac{1}{2}\sum_{i=1}^{d}(t_i)^2}$, $\theta_{2}=n^{-1}\sum_{i=1}^{d}(t_i)^2$, and $\phi_{2}(K)=\int |K(x)|^2 dx$. It can be shown that the estimator $\hat{M}(h)$ is asymptotically unbiased (up to a constant shift) for estimating $M(h)$, where $\hat{M}(h)=A+B-C$ with the quan-

<table>
<thead>
<tr>
<th>Density</th>
<th>$n = 50$</th>
<th>$n = 400$</th>
<th>$n = 900$</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>$\hat{M}(h_{1c})$</td>
<td>0.00(1x10^{-4})</td>
<td>0.002(2x10^{-6})</td>
</tr>
<tr>
<td></td>
<td>$\hat{M}(h_{2c}) / \hat{M}(h_{1c})$</td>
<td>1.03(1.13)</td>
<td>1.11(0.97)</td>
</tr>
<tr>
<td>#2</td>
<td>$\hat{M}(h_{1c})$</td>
<td>0.08(2x10^{-6})</td>
<td>0.02(2x10^{-4})</td>
</tr>
<tr>
<td></td>
<td>$\hat{M}(h_{2c}) / \hat{M}(h_{1c})$</td>
<td>1.00(0.95)</td>
<td>1.06(0.74)</td>
</tr>
<tr>
<td>#3</td>
<td>$\hat{M}(h_{1c})$</td>
<td>0.021(3x10^{-6})</td>
<td>0.004(8x10^{-6})</td>
</tr>
<tr>
<td></td>
<td>$\hat{M}(h_{2c}) / \hat{M}(h_{1c})$</td>
<td>1.00(1.03)</td>
<td>1.07(1.43)</td>
</tr>
</tbody>
</table>

Note: For each $n$ (100 replications in each case), the sample mean of $\hat{M}(h_{1c})$ and the ratio of the sample mean of $\hat{M}(h)$ to that of $\hat{M}(h_{1c})$ for $h_1$ and $h_2$ are given. For each density and $n$, the value inside the first pair of parentheses is the estimated standard error of $\hat{M}(h_{1c})$, and the values inside the second and third pairs of parentheses are the ratio of the estimated standard error of $\hat{M}(h)$ to that of $\hat{M}(h_{1c})$, for $h_1$ and $h_2$, respectively.

Table 2. Simulation results for variable kernel estimation of bivariate density #1 to #2

<table>
<thead>
<tr>
<th>Density</th>
<th>$n = 100$</th>
<th>$n = 400$</th>
<th>$n = 900$</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>$\hat{M}(h_{1c})$</td>
<td>0.008(2x10^{-4})</td>
<td>0.002(2x10^{-6})</td>
</tr>
<tr>
<td></td>
<td>$\hat{M}(h_{2c}) / \hat{M}(h_{1c})$</td>
<td>1.17(1.12)</td>
<td>1.30(4.36)</td>
</tr>
<tr>
<td>#2</td>
<td>$\hat{M}(h_{1c})$</td>
<td>0.004(2x10^{-4})</td>
<td>0.001(3x10^{-6})</td>
</tr>
<tr>
<td></td>
<td>$\hat{M}(h_{2c}) / \hat{M}(h_{1c})$</td>
<td>1.07(0.93)</td>
<td>1.18(1.46)</td>
</tr>
<tr>
<td>#3</td>
<td>$\hat{M}(h_{1c})$</td>
<td>0.10(2.34)</td>
<td>1.18(3.95)</td>
</tr>
</tbody>
</table>
\[ A = (2\pi)^{-d} \int_\mathbb{R} \left[ \hat{f}(t) \right]^2 \cdot \left( 1 - \frac{1}{h_{\text{opt}}(t)} \right)^2 \, dt \]

\[ B = (2\pi)^{-d} \int_\mathbb{R} \left( h^d \right) \sigma^2(\mathbf{K}) \, dt \]

\[ C = (2\pi)^{-d} \frac{n}{\sum_i h_i^d \left( \frac{\hat{h}(t)}{h_i} \right)^2} \, dt \]

Here \( \hat{R} = \left[ \hat{r}_{11}^*, \hat{r}_{12}^*, \ldots, \hat{r}_{d,1}^*, \hat{r}_{d,2}^* \right] \) is the d-dimensional random rectangular and \( \hat{R}^* \) is the cut-off frequency proposed by Wu and Tsai (2004). Let \( h_0 \) denote the unknown true minimizer of \( M_{\text{true}}(h) \), i.e., \( h_0 \) is the unknown optimal global smoothing parameter. We propose to use the minimizer \( \hat{h}_{\text{opt}} \) of \( M_{\text{true}}(h) \) to estimate \( h_0 \).

We have carried out extensive simulation studies to compare the performance of our variable bandwidth selector \( \hat{h}_{\text{c}} = \hat{h}_{\text{opt}} \) with \( \hat{h}_{\text{a}} \) (the square-root method of Abramson, 1982) and \( \hat{h}_{\text{b}} \) (the binned method of Sain and Scott, 1996, for d=1 and Sain, 2002 for d=2). Here \( b \) is the local bandwidth factor selected by our average cluster method. Throughout we use the Gaussian kernel due to its numerical and intuitive advantages, and all the minimizers are obtained by searching over \( h \in (0,2] \).

One hundred replication of data sets of various sizes \( n \) are generated from each of the three univariate normal mixture densities: (1) \( N(0,1) \); (2) \( N(0,1,1,1) \); (3) \( \text{(strongly skewed)} \)

\[ \{1/8 \sum_{i=1}^{10} M \left( \frac{1}{2} \left( \sqrt{2}/3 \right)^i - 1 \right), (2/3)^i \} \]

(separated bimodal) \( 0.5N(-3/2,1/4) + 0.5N(3/2,1/4) \); and the two bivariate normal mixture densities: (1) \( N(0,0,1,1) \); (2) \( N(-6/5,0,1,1,0) + 0.5N(6/5,0,1,1,0) \). The sample sizes considered here are \( n=50,400,900 \) for \( d=1 \), and \( n=100,400,900 \) for \( d=2 \). All random samples are generated by the function RAND in FORTRAN. For each sample we apply the fast Fourier transform to evaluate the sample characteristic function.

For comparing the performance of selectors, say \( \hat{h} \), we choose to compare \( \hat{M}(\hat{h}) \), as the sample mean of the MISE \( M(\hat{h}) \). Tables 1-2 summarize the results. They show for both \( d=1 \) and 2 and all densities considered: (i) the proposed \( \hat{h}_{\text{c}} \) performs overwhelmingly well at every \( n \), with the mean MISE being the smallest throughout and (ii) as \( n \) increases, the sample mean of \( M(\hat{h}_{\text{c}}) \) decreases to 0 at a very fast rate, and this rate is faster than that of the sample mean of \( M(\hat{h}_{\text{a}}) \) for both \( \hat{h}_{\text{a}} = \hat{h}_{\text{a}} \) and \( \hat{h}_{\text{a}} = \hat{h}_{\text{b}} \). Therefore, \( \hat{h}_{\text{c}} \) seems to be fairly reliable for many practical situations.

It should be noted that the sample variation of \( M(\hat{h}_{\text{a}}) \) is the largest for most of the cases under consideration. For all three univariate densities the sample variations of \( M(\hat{h}_{\text{c}}) \) and \( M(\hat{h}_{\text{b}}) \) are comparable, while the former is smaller than the latter for univariate densities #1 and #3, and larger than the latter for univariate density #2. For both bivariate densities the sample variation of \( M(\hat{h}_{\text{c}}) \) is essentially the smallest at \( n=400 \) and 900, and comparable with that of \( M(\hat{h}_{\text{a}}) \) at \( n=100 \).

Although in the paper we are not able to provide theoretical results concerning, for example, the asymptotic bias and MISE of the proposed method due to some technical difficulty, the simulation results demonstrate that the proposed method performs superiorly and is therefore very promising. Our future study will include: (i) establishing the aforementioned theoretical results and (ii) extending our method to the investigation of variable bandwidth selection in kernel estimation of density (partial) derivatives and to the estimation of integrated squared density (partial) derivatives.
Telomerase, a ribonucleoprotein enzyme involves in the synthesis and maintenance of telomeric repeats in the ends of chromosomes, is expressed in immortalized cell lines and in approximately 90% of human malignancies, but not in most adult somatic tissues. The human telomerase reverse transcriptase (hTERT) is the catalytic subunit for human telomerase and its expression is highly associated with telomerase activity. Telomerase activity and hTERT mRNA expression are detected in most, if not all, cancers including bladder cancer. By contrast, normal tissues, including those adjacent to cancer, display no or very low levels of telomerase activity. Moreover, the levels of hTERT expression are significantly associated with bladder tumor grade and stage. Therefore, hTERT may serve as a good target for gene therapy of bladder cancer and also be useful for targeted transgene expression in human and murine cancers. The use of hTERT promoter-driven vector system is able to restrict transgene expression to telomerase-positive tumors. Because the vast majority of human bladder cancers express telomerase activity, the hTERT promoter may be exploited for bladder tumor-specific transgene expression in gene therapy of bladder cancer.

Etoposide causes DNA strand breaks and induces apoptosis in a variety of tumor cells. Etoposide upregulates telomerase activity in human pancreatic cancer cells. Furthermore, etoposide at clinically acceptable dosages suppresses humoral and cellular immune responses to adenoviral vectors, thereby enhancing intratumoral transgene expression. We hypothesized that low-dose etoposide can increase the infection efficiency of adenoviral vector encoding cytosine deaminase (CD) under the transcriptional control of the hTERT promoter and enhance CD gene expression through upregulation of the hTERT promoter activity in telomerase-positive bladder cancer cells. Here we demonstrate that low-dose etoposide increased the hTERT promoter activity through upregulation of hypoxia-inducible factor (HIF)-1α expression and enhanced adenoviral infection via upregulation of coxsackie-adenovirus receptor (CAR) in bladder cancer cells. Therefore, the combination of etoposide and adenovirus-mediated CD gene therapy driven by the hTERT promoter may have potential applications for the treatment of bladder cancer or other telomerase-positive malignancies.

Fig. 1. Low-dose etoposide upregulated the expression of CAR on bladder cancer cells. J82 and TCC-SUP cells were cultured in the presence or absence of etoposide (0.1 μg/ml) for 6 h and analyzed for surface expressions of CAR as well as αvβ3 and αvβ5 integrins by flow cytometry. Thick line indicates etoposide-treated and dotted line indicates untreated cells incubated with respective monoclonal antibody. Thin line indicated untreated cells incubated with isotype IgG1 for background
staining. For each panel, the top number (+) indicates the mean fluorescence intensity for the etoposide-treated cell population, whereas the bottom number (-) is the untreated population.

Low-dose etoposide enhanced adenovirus infection through upregulation of CAR but not αvβ3 or αvβ5 integrins on bladder cancer cells. Efficient adenovirus infection requires CAR and αvβ integrins for attachment and internalization to enter host cells. As shown in Fig. 1, J82 cells expressed moderate levels while TCC-SUP cells expressed high levels of CAR. However, both cells expressed little αvβ3 and αvβ5 integrins. Furthermore, etoposide enhanced CAR expression on both cells, but had little effects on αvβ3 and αvβ5 integrin expression. The increase of cell surface CAR may have led to increases in transgene expression and subsequent protein production. We also confirmed that the increased CAR allowed increased adenovirus entry into cells. In J82, TCC-SUP, MBT-2, and NIH3T3 cells, etoposide treatment enhanced β-gal activities in Ad-LacZ-infected cells (Fig. 2),

Fig. 2. Low-dose etoposide enhanced adenovirus infection on bladder cancer cells. J82, TCC-SUP, MBT-2, and NIH3T3 cells were infected with Ad-LacZ at an MOI of 1 or 10 with or without etoposide (0.1 μg/ml) for 6 h. After 42 h, β-gal activity in the cell lysate was determined and expressed in relative light units per microgram protein. Data shown were the mean ± S.D. of three determinations, which were consistent in two separate experiments.
h. After 42 h, β-gal activity in the cell lysate was determined and expressed in relative light units per microgram protein. Data shown were the mean ± S.D. of three determinations, which were consistent in two separate experiments.

Suggesting that enhanced efficiency of adenoviral transgene expression by etoposide treatment may have been attributed, in part, to the upregulation of CAR expression. Notably, not only bladder cancer cells but also NIH3T3 fibroblasts became more susceptible to adenoviral infection after etoposide treatment. Therefore, low-dose etoposide consequently enhanced cytotoxic activity of recombinant adenovirus with CD gene driven by hTERT promoter in combination of treatment with 5-fluorocytosin (5-FC) in various bladder cancer cells and had only negligible effects on cell survival in NIH3T3 cells regardless of treatment with etoposide. Although Ad-hTERT-CD alone followed by 5-FC treatment slowed tumor growth in MBT-2 tumor-bearing mice, the survival rate was enhanced only from 0% to 30%. Based on the in vitro data described above, we sought to enhance the therapeutic effect of Ad-hTERT-CD/5-FC by combination with low-dose etoposide. The severe side effects of 5-FC, including hepatotoxicity and bone-marrow depression, are concentration-dependent and can be elicited by many other agents, such as immunosuppressive or cytostatic agents. As shown in Fig. 3.

![Figure 3](image_url)

**Figure 3.** Ad-hTERT-CD/5-FC in combination with low-dose etoposide synergistically suppressed tumor growth and prolonged survival in mice bearing syngeneic MBT-2 tumors. Groups of 8 tumor-bearing mice were treated with Ad-hTERT-CD (10^8 or 10^9 PFU) intratumorally at days 11, 12, and 13 followed by 5-FC (200 mg/kg) treatment for 7 consecutive days starting on day 12, or with etoposide (2 mg/kg) for 8 consecutive days starting on day 11 alone or in combination. The mean tumor volume ± S.D. [p=0.0001, 0.0001, and 0.0002 for Ad-hTERT-CD (10^8)/etoposide, Ad-hTERT-CD (10^9)/etoposide, and Ad-hTERT-CD (10^9) versus etoposide, respectively; p=0.0002 and 0.0016 for Ad-hTERT-CD (10^8)/etoposide and Ad-hTERT-CD (10^9)/etoposide versus Ad-hTERT-CD (10^9), respectively] (A) and the Kaplan-Meier survival curves [p=0.0001, 0.0001, and 0.0003 for Ad-hTERT-CD (10^8)/etoposide, Ad-hTERT-CD (10^9)/etoposide, and Ad-hTERT-CD (10^9) versus etoposide, respectively; p=0.0003 and 0.0005 for Ad-hTERT-CD (10^8)/etoposide and Ad-hTERT-CD (10^9)/etoposide versus Ad-hTERT-CD (10^9), respectively] (B) are shown.
hTERT-CD (109), respectively] (A) and the Kaplan-Meier survival curves [p=0.0001, 0.0001, and 0.0003 for Ad-hTERT-CD (109)/etoposide, Ad-hTERT-CD (108)/etoposide, and Ad-hTERT-CD (109) versus etoposide, respectively; p=0.0003 and 0.0005 for Ad-hTERT-CD (109)/etoposide and Ad-hTERT-CD (108)/etoposide versus Ad-hTERT-CD (109), respectively] (B) are shown.

While low-dose etoposide had no antitumor effects, Ad-hTERT-CD/5-FC (109 PFU) alone retarded tumor growth (p=0.0002) and prolonged survival (p=0.0003) in MBT-2 tumor-bearing mice compared with etoposide treatment alone. Ad-hTERT-CD alone inhibited tumor growth by 22 days, with regrowth of tumors thereafter when 5-FC was no longer administered. Remarkably, Ad-hTERT-CD (109 PFU)/5-FC in combination with etoposide synergistically suppressed tumor growth and enhanced survival in tumor-bearing mice compared with either Ad-hTERT-CD/5-FC (p=0.0002 for tumor volume and p=0.0003 for survival) or etoposide (p=0.0001 for tumor volume and p=0.0001 for survival) treatment alone. Therefore, high- and low-dose Ad-hTERT-CD/5-FC in combination with low-dose etoposide induced complete tumor regression in 75% and 50% of tumor-bearing mice and generated antitumor immunity, respectively. As shown in Fig. 4, H&E stain reveals necrosis within tumors from mice treated with Ad-hTERT-CD/5-FC alone. Furthermore, Ad-hTERT-CD/5-FC plus etoposide induced more tumor necrosis. Immunohistochemical staining demonstrates that CD4+ and CD8+ T cells that infiltrated tumors were significantly increased in the combination treatment group compared with those in the remaining groups. These results suggest that activated immune cells within tumors may have contributed to higher antitumor effects of the combination regimen.

As etoposide is widely used in the clinical settings, it serves as a feasible activator to enhance the therapeutic index of hTERT promoter-driven suicide gene therapy. Because a majority of human tumors exhibit high telomerase activity, adenovirus-mediated CD gene therapy driven by the hTERT promoter in combination with low-dose etoposide may be applicable to a broad spectrum of cancers.

Figure 4. Ad-hTERT-CD/5-FC in combination with low-dose etoposide synergistically suppressed tumor growth and prolonged survival in mice bearing syngeneic MBT-2 tumors. In a separate experiment, tumors were excised from the treated mice at day 21 and subjected to H&E stain and immunohistochemical stain for detecting infiltrating CD4+ and CD8+ T cells that were stained red within tumors.
Introduction

Organic thin film transistors (OTFTs) are widely investigated by scientists because potential advantages offered by the films such as easy processing, simple structure, and low process temperature. Recently, several research groups have successively demonstrated prototype active-matrix display, each pixel of which is driven by poly(3-hexylthiophene) (P3HT) transistors. The results of the experimental studies have drawn considerable attention due to ease of solution process, and low cost of fabrication such as spin coating, dip coating, ink-jet printing and rubber stamp printing of P3HT semiconductor layer.

In active matrix display technologies, the pixel structure generally includes a single thin-film transistor (TFT) and one storage capacitor. One of the criteria determining the driving OTFT in pixel is the leakage current that flows through the capacitor during off state. This phenomenon allows a capacitor to discharge and reduces its hold voltage. Aforementioned conditions influence brightness and contrast parameters of the display. In previous studies, one of the suppression methods of OTFT leakage current was to adopt different work function metal material to serve as the source/drain electrodes. One of electrodes could form a schottky barrier between metal and organic semiconductors that would decrease the carrier injection from metal to semiconductor thus leading to low leakage current during off state as well as lower carrier mobility during on state.

In this chapter, the KrF excimer laser was used to treat one of the indium-tin-oxide (ITO) source/drain electrodes of the OTFTs. After the treatment, the work function of ITO has increased. Using the method described above, we were able to fabricate a OTFT device with different work function source and drain electrodes, which could effectively suppress the device leakage current, simplify the process, and maintain carrier mobility.

Active display drive technologies

Figure 1 show the equivalent circuit for a pixel in a TFT LCD panel. The liquid crystal layer and a storage capacitor are connected in parallel, as load to the TFT. The TFT turns on when a positive voltage pulse is applied to the gate electrode. As a result, the signal voltage can be transmitted to the drain and, subsequently, to the liquid crystal layer and the storage capacitor that are connected as load to the TFT. During this operation, the pixel voltage rise with the gate pulse, up to a maximum that, ideally, equals the source
electrode voltage. This voltage will than be maintained in the pixel throughout the frame time, until an -
other gate voltage pulse changes the state of the pixel.

Fig. 2 P3HT-based OTFT structure: (a) a glass substrate with patterned ITO electrode, functions as a gate, and SiO2 (300 nm) is the gate dielectric. Photolithographically defined ITO electrodes function as source and drain on top of the dielectric. (b) One of the ITO electrodes irradiated with excimer laser and the other shadowed by a metal mask. (c) Laser irradiated and native ITO electrodes denote A and B, respectively. (d) Organic semiconductor, P3HT, inkjet-printed on top of A and B electrodes and SiO2 dielectric to complete bottom-contact OTFT fabrication.

Experimental
An ITO coated glass substrate was used for the experiments described in the study. ITO films were photolithographically patterned to serve as the gate electrodes of OTFT devices. A 300 nm silicon dioxide (SiO2) layer, acting as the gate insulator, was deposited by physical vapor deposition onto the ITO substrate. Then, the ITO source-drain electrodes were deposited to form an electrode on the surface of the SiO2 film through photolithography and etching, resulting in a channel that was 30 μm long and 500 μm wide, as shown in Fig. 2(a). In order to remove unintentional organic residue, the surfaces of the ITO electrodes and SiO2 dielectrics were then cleaned using oxygen (O2) plasma with power of 500 W at zero bias, held at 3 min. After O2 plasma cleaning, a metal mask was used to shadow one of the ITO electrodes, while the other ITO electrode was irradiated with a KrF excimer laser with pulse duration of approxi-
mately 50 ns. The wavelength of the laser was 248 nm. The laser irradiation was applied for 15 min, as shown in Fig. 2(b). The incident laser dose was equal to 26 mJ/cm2, the repetition rate was 50 Hz. Figure 2(c) shows that the excimer laser irradiated electrodes and native ITO electrodes were marked as “A” and “B”, respectively. Later, P3HT (regioregularity ~ 98.5%, purchased from Aldrich Chemical Co.) was dissolved in p-xylene with concentration of 0.25 wt% and then inkjet printed on the substrate in air ambience to complete a bottom-contact OTFT, as shown in Fig. 2(d). The devices were later baked at 120 °C for 1 hour in a vacuum oven after the inkjet printing process. Experimental conditions of gas-pressure driven printing head were 150μm-diameter syringe needle and 0.1 kg/cm2 - 0.01 s-pressure nitrogen to drop P3HT.

P3HT in OTFT devices behaves as a p-type semiconductor. Typically, the drain current, IDS, is measured and plotted against the drain voltage, VDS, at different gate voltage levels, VGS. When the gate electrode is biased negatively with respect to the grounded source electrode, P3HT OTFTs operate in the accumulation mode and the accumulated charges are holes. The IDS versus VDS curves were obtained in vacuum conditions by scanning VGS using a Keithley 4200-SCS semiconductor characterization system.

Result and Discussion
Figure 3 shows the output characteristics (IDS – VDS) of two OTFT devices, L1 (closed circles) and L2 (open circles). The L1 device had KrF excimer laser irradiated ITO source electrode marked as “A” electrode and native ITO drain electrode marked as “B” electrode. However, the type of the source and drain electrodes in L2 device is opposite to the type of the source and drain electrodes in L1, as listed in Table 1.

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comparison purposes, we fabricated L3 device with native ITO source and drain electrodes with the same structure that is included in Table 1. As shown in Fig. 3, the magnitude of IDS produced by the L1 device is significantly larger than that of the L2 device. In Fig. 4, the ITO surface of the source, irradiated for 15 minutes, shows a reduction in the root-mean-square surface roughness (Rrms). The reduction of 0.17 nm was observed as compared to the non-irradiated ITO surface. The decrease in Rrms of the ITO in L1 device may results in reduced trap state density between source and the P3HT layer. Therefore, an increase in injected IDS in the L1 device can be attributed to low trap density in P3HT/ITO interface. Consequently, the injection current, IDS, can be dramatically enhanced by excimer laser treatment method. Moreover, Fig. 3 reveals that a significantly enhanced IDS takes place at lateral electric field (VDS ranging from 0 V to -60 V) for device L1. This result implies formation of an ideal contact (ohmic contact) at laser-irradiated source/P3HT interface. Contrary, the L2 device has a non-ideal contact at source/P3HT.

Figure 5 shows a plot of the square-root and logarithm of IDS as a function of VGS for these OTFTs. The L1 device with A/B serving as the source/drain shows better performance than other devices. By fitting the data to saturation regime (between -50 and -80 V of VGS) standard field-effect transistor equations, obtained electrical parameters, including μsat, threshold voltage (Vth), sub-threshold swing (SS), and on/off ratio, for all devices are listed in Table 1. The μsat of the L1 device is slightly better than the L2 and L3 devices. The similar μsat for all devices indicated that the organic semiconducting materials it-

Interestingly, Fig. 5 shows that the OFF-state leakage current, IOFF, of L1 device is two orders lower than those of L2 and L3 devices under depletion mode measurements for the gate potential ranging from 1 to 60 V. These depletion mode measurements were used to characterize IOFF variations at the source side under the drain potential of -60 V with respect to source in the output and transfer characteristic measurements. Lower value of IOFF variations could be observed at reverse biases, while slight IOFF increase occurred at VGS > 55 V for the L1 device. The saturated IOFF originates from local electrons located at the vibration states near the highest occupied molecular orbit (HOMO) of P3HT and accumulated at the channel/bottom oxide interface near source under reversed biases. To investigate the mechanism of the improved performance for the L1 device the HOMO of P3HT and the work functions of A and B electrodes were measured by photoelectron spectrometer (AC-2, Riken-Keiki Co.). The lowest unoccupied molecular orbital (LUMO) of P3HT was determined using the optical gap of 1.7 eV, as determined from optical absorption. Detailed band-diagram of the L1 device is presented in Fig. 6.

The ITO surface of the source irradiated for 15 minutes shows an increase in work function by 0.7 eV. Because of high source/channel barrier induced by KrF excimer laser
irradiation and electrons under the condition of reversed gate bias, the lowest IOFF value was obtained in the L1 device. Additionally, as presented in Table 1, the L1 device had the largest IDS rectification ratio of 10 to -10 V under zero gate bias through the higher barrier in source electrodes. Therefore, KrF excimer laser irradiation on the surface of source could suppress the OFF current effectively. For OTFTs, the device switching performance proportional to the square of channel length, decreases rapidly along with decrease in channel length. However, the switching performance of the device with excimer laser irradiated source was two orders higher than normal device even with a short channel length. This is an important factor for miniaturization of organic-based TFTs.

**Conclusion**

In summary, this study demonstrates innovative OTFTs with asymmetrical work function electrodes created by KrF excimer laser irradiation. The increase of work function and reduction of surface roughness in ITO source electrodes were achieved using KrF excimer laser, which plays a positive role in enhancing on/off ratio and reducing sub-threshold swing of OTFTs. Moreover, high electrode/channel barriers created by excimer laser irradiation could block local electrons, accumulated at the channel/gate dielectric interface near the source. The barriers played an important role in lowering the IOFF value by up to two orders in the reversed mode measurements. Furthermore, we would like to note that treatment method of KrF excimer laser plays an important role in minimizing the size of OTFTs.

**Reference**


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**Table I.** Device performance of P3HT-OTFTs with various work function source and drain electrodes. A and B electrodes represent the excimer laser irradiated and native ITO electrodes, respectively.

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Source/Drain electrodes</th>
<th>Mobility (cm²/Vs)</th>
<th>Subthreshold swing (V/dec.)</th>
<th>$V_T$ (V)</th>
<th>$I_{ON}/I_{OFF}$ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>A/B</td>
<td>$2.29 \times 10^{-3}$</td>
<td>2.54</td>
<td>-11.17</td>
<td>$1.0 \times 10^5$</td>
</tr>
<tr>
<td>L2</td>
<td>B/A</td>
<td>$1.83 \times 10^{-3}$</td>
<td>8</td>
<td>-22.33</td>
<td>$9.1 \times 10^2$</td>
</tr>
<tr>
<td>L3</td>
<td>B/B</td>
<td>$2.04 \times 10^{-3}$</td>
<td>7.24</td>
<td>-15.52</td>
<td>$2.8 \times 10^3$</td>
</tr>
</tbody>
</table>

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**Figure 5** Source-drain current versus gate voltage at $V_{DS} = -60$ V for P3HT OTFTs with A electrode as source electrode (close circles) and B electrode as source electrode (open circles).

**Figure 6** The schematic band diagram for P3HT OTFT with A and B electrodes.
NCKU Alumni Return on the 76th School Anniversary and Donate 100 Thousand US Dollars

To recall the reminiscences of the old days in university, a group of 158 alumni, who are over 70 years old, came from around the world to celebrate the 76th anniversary of their alma mater. In addition, they also donated $100,000 US dollars (approx. $3,200,000 NTD) to help building “Si-Yuan Hall (思源堂)”. With the accompany of Mao-Jung Yeh (葉茂容), Director of Alumni Association Center, the alumni toured the old department buildings of Electrical Engineering, Mechanical Engineering, Chemical Engineering and Mining & Metallurgical Engineering at Cheng-Kung Campus and the old library at Sheng-Li Campus. They had such a good time that no one wanted to part when the tour came to an end.

Fifty years are not a short time, so the feelings were complicated when those 158 alumni finally got together again at their alma mater 50 years after they left the school. It felt sweet yet melancholy when they saw the long hallway in the old department building, and the corner from memory. They could still find the spot where a few of good friends used to hang out. The trees in front of the department buildings had grown so big that they could hardly recognize. A bittersweet feeling swelled.

Back in 1957, the whole university only consisted of six departments: Electrical Engineering, Civil Engineering, Mechanical Engineering, Chemical Engineering, Mining & Metallurgical Engineering and Architecture. There were not many students and most classrooms were located in the buildings at Cheng Kung Campus. The dormitories and the library were at Sheng-Li Campus. The school was not big but the students had more chances to get together and develop long-standing friendship. It had been 50 years, and the time only seemed not enough for them to catch up on.

Director Yeh of Alumni Association Center stated that Ju-Liang Wang (王汝樑) and Jie-Chun Tian (田介純), graduate of Civil Engineering and Architecture of 1957, were a loving couple whom many people envied. When they learnt that NCKU was planning a budget for the building of “Alumni Center”, they immediately called a fund-raising event and received a rapid and enthusiastic response at the 6th Reunion for the Alumni of 1957. They raised $100,000 USD in total and decided to give it all to assist their alma mater with the building of “Si-Yuan Hall” in the Alumni Center.

Unfortunately, alumnus Ju-Liang Wang passed away last summer. Mrs. Jie-Chun Tian took upon herself the responsibility to fulfill Wang’s will. She returned to NCKU on November 11th, the day of the 76th Anniversary of NCKU, and represented the alumni of 1957 to donate this $100,000 USD (approx. $3,200,000 NTD) to buy equipment and software for the Alumni Center.

In addition, Mr. Chi-Hong Chen (陳治宏), graduate of Electrical Engineering of 1967, is now President of the Alumni Association in North America (北美校友會聯合會). Chen launched an EAU plan (Enterprises-Alumni-University) in response to NCKU’s goal of becoming a top university in the world. He encouraged all the alumni in North America to actively participate in and contribute to NCKU with their international experiences in academia, industry, professional and government. Only through the participation, the connections between the alumni and their alma mater can be strengthened. By holding reunion events and awarding outstanding alumni, they can promote comprehensively the development of professions and the collective performance of the alumni in the world.

For the list of alumni of 1957 attending the 76th anniversary, please refer to the Chinese Version.

Professor Huan-Yao Lei Appointed to the Newly Created Position of Asian Editor for Experimental Biology and Medicine

The Editor-in-Chief of Experimental Biology and Medicine (EBM), Dr. Steven R. Goodman, has delineated a plan for expansion of the journal and enhancement of the activities of the Society of Experimental Biology and Medicine (SEBM) into Asia. The plan, which is strongly supported by the SEBM Council, involves bringing outstanding Asian researchers onto the EBM Editorial Board, naming Associate Editors from amongst the leaders in Asian Biomedical Science, and then selecting an individual to become the first Asian Editor for EBM. EBM has added Professor Lin He as co-Associate Editor for the
EBM Endocrinology and Nutrition section and Professor Huan-Yao Lei as co-Associate Editor for the Immunology/Microbiology/Virology section. EBM has also added Professors Qingming Luo (Bioimaging), Xintao Shuai (Biomedical Engineering), Huiqi Xie (Biomedical Engineering), Shaw-Jeng Sean Tsai (Physiology) and Chunyu Zeng (Physiology) to the Editorial Board.

Dr. Goodman is now announcing the appointment of the seminal EBM Asian Editor: “It is my great pleasure to announce that effective January 1, 2008 Professor Huan-Yao Lei has been appointed to the newly created position of Asian Editor for Experimental Biology and Medicine. Huan-Yao Lei is a Professor in the Department of Microbiology and Immunology, and Chairman of the Institute of Basic Medical Sciences at the College of Medicine of the National Cheng-Kung University (NCKU) of Taiwan. From 1982 to today, Huan-Yao has published 165 peer reviewed articles primarily in the area of microbiology and virology. He is a leading Asian scientist whose current interests deal with the dengue virus.”

A new Asian office for Experimental Biology and Medicine will open at the NCKU Medical Center with an inaugural ceremony on January 7, 2008. Dr. Lei, with his editorial assistant, will play an essential function towards the goal of creating an international presence for EBM in Taiwan. It has 9 colleges, spanning engineering to the social sciences and 22,000 students. It has a powerful College of Medicine which will be the home of our new EBM Asian office. Dr. Charles Lin, Dean of the College of Medicine at NCKU, said the following concerning the establishment of the Asian EBM office at NCKU Medical Center: “By establishing its first Asian Office, the Society of Experimental Biology and Medicine has built a bridge to the scientific society in Asia and a highway of sharing ideas, news and discovery of health science.”

NCKU is one of the largest, oldest, and most prestigious universities in Taiwan. It has 9 colleges, spanning engineering to the social sciences and 22,000 students. It has a powerful College of Medicine which will be the home of our new EBM Asian office. Dr. Charles Lin, Dean of the College of Medicine at NCKU, said the following concerning the establishment of the Asian EBM office at NCKU Medical Center: “By establishing its first Asian Office, the Society of Experimental Biology and Medicine has built a bridge to the scientific society in Asia and a highway of sharing ideas, news and discovery of health science.”

Dr. Goodman stated “The establishment of our Asian Editor Professor Lei, and the Asian EBM office, is the first step in our globalization plan for EBM and SEBM. We have begun the process of developing a similar Editor position and office in Europe.” In discussing the impact of these announcements upon EBM and the SEBM Dr. Burt Sobel, President of SEBM, stated “Under the vigorous and creative leadership of Dr. Steven R Goodman, the Editor-in-Chief of Experimental Biology and Medicine, the journal of the Society of Experimental Biology and Medicine, the scope of the journal and of the society itself is expanding profoundly. Two seminal events give credence to the progress being made, namely the appointment by Dr. Goodman of Dr. Lei Huan-Yao as the first Asian Editor for the journal coinciding with the opening of an Asian office that will support Dr. Huan-Yao’s efforts and editorial activities of the Journal in Asia on January 7, 2008. Together these initiatives will strengthen the scientific thrust and robustness of the journal thereby enhancing its impact and the strength of the Society throughout the world. We look forward to presenting and widely distributing the outstanding science being undertaken by our colleagues in Asia.”

Experimental Biology and Medicine is a journal dedicated to the publication of multidisciplinary and interdisciplinary research in the biomedical sciences. The journal was first established in 1903. Experimental Biology and Medicine is the journal of the Society of Experimental Biology and Medicine. To learn about the benefits of society membership visit www.sebm.org. If you are interested in publishing in the journal please visit www.ebmonline.org.