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Optical Techniques for Future Pacemaker Technology

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1. Introduction

Current muscle pacemaker technology mostly relies on electrical techniques. The electrical method is well understood and established, however, the electricity is difficult to localize and has a risk of interfering with intact cells, tissues, and organisms, affecting their electrophysiology.

Light has the potential to be a novel medium in future pacemaker technology. Light is typically minimally invasive and has low interactivity with biological tissues. Depending on the wavelength, this unique property allows its use to access deep inside biological tissues and opens up potential extension of light and photonics technology to a variety of applications in biosciences, such as in vivo manipulation of biological functions. Combined with nonlinear optical technology, only light technology allows location-selective manipulation deep inside tissues with minimum disturbance to the surrounding areas. Other light properties, such as an inherent sterility and the fact that it does not interfere with measurement instruments, makes the technology attractive.

In this chapter, we describe light-based techniques that may be used for future muscle pacemaker technology. Recently we presented femtosecond laser pacemaker for heart muscle cells through nonlinear light technology. This chapter describes details of light interaction with cells and in particular muscle cells, including experimental and modeling studies. Besides nonlinear light technology, other light-based techniques for manipulating muscle activities are reviewed. These techniques may not be able to pace muscle activities, but are still worth considering since they can change the beat rate. In the latter part, this chapter also includes indirect light-tissue interactions mediated by implanted pacemaker devices, such as rechargeable battery and transcutaneous telemetry systems for both deliverying power to an implanted pacemaker and also for monitoring pacemaker function. The light-driven and light-mediated implanted devices may in the future play an important role in developing implanted pacemaker technology.

Light-based pacemaker technology has just started recently and the interaction effect is partially unclear and needs to be studied more precisely. The light-based technology, however, has significant and perhaps surprising potential for pacemaker technology. In the future, light-based techniques may not only shed light on the future development of pacemaker technology but can also help understandings of basic underlying science in fatal

cardiac arrhythmia caused by unexpected local distortion of the beating rhythm, which can also be controlled by light.

2. Overview of light-tissue interactions for pacemaker technology

2.1 Slow acting or non-localized approach to optical pacing

Light typically has low interactivity with biological tissues. Depending on the wavelength, this unique property allows its use to access deep inside biological tissues and opens up potential extension of light and photonics technology to a variety of applications in biosciences, such as in vivo manipulation of biological functions. Additionally, light is inherently sterile, reducing the chance of infectious deseases.

Through the interaction with pigments, such as flavin and cytochrome C (Karu, T, 1999) in the visible spectral range, and aromatic compounds and water in the ultraviolet (UV), light can efficiently manipulate biological tissues. Manipulation based on linear absorption by chromophores is reported for different types of cells. The nerve cell is one of the most frequently studied types of cells regarding light-based manipulation technology and photostimulation of nerve cells by both visible (Fork, 1971) and UV (Oxford & Pooler, 1975; Schwarz and Fox, 1977) light excitation are reported. In these papers, the electrical activity is manipulated by laser exposure. In mast cells, an increase in calcium ion concentration by visible light exposure has been shown (Yang *et al*., 2007). The calcium ion plays crucial and different roles in many types of cells, and light-based calcium manipulation is then one compelling indicator of the potential for light technology to stimulate and control biological functions.

Regarding the pacing of muscle beating, several studies have been carried out, which are not directly pacemaker technology, but still have potential to modulate the muscle contraction activity. Gimeno *et al*. first reported the acceleration of heart beating rate by exposure to visible light (Gimeno *et al*., 1967). They simply measured the beat rate of 2-5 day old embryo chick heart cells while changing the illumination intensity (set to high or low) and isolating the irradiation from different wavelength ranges between 450 and 650 nm. The heart beat rate is modified by changing the illumination intensity. Interestingly, this switching seems to be reversible in their report. Salet *et al*. showed an increase in the beating rate of myocardial cells following laser irradiation under the absence of ATP in culture medium (Salet *et al*., 1979). Alteration of membrane electrical activity in rat myocardial cells as well as changes in the contractility by laser irradiation was also demonstrated (Kitzes *et al*., 1977). Nathan *et al*. showed that UV (260-310 nm) illumination could also modulate the beat rate of embryo chick heart cells as well as the electrical properties (Nathan *et al*., 1976). In their measurement, the heart beat rate was increased to a maximum plateu level, up to approximately 200% of the original frequency, followed by fatal cessation, over a one minute time scale. Salet at al. reported a temporary increase in the beating frequency of myocardial cells due to UV (254 nm) micro-irradiation of the cytoplasm, especially mitochondria (Salet *et al*., 1976), although it should be noted that using UV irradiation does not allow for the precise targeting of particular parts of the cell since photons are linearly absorbed throughout the focused light cone. A recent study also shows that near UV radiation modifies the membrane sodium current in Guinea-pig ventricular myocytes (La *et al*., 2006).

The issue of these light interactions for pacemaker technology is the use of single photon absorption and usually a corresponding interaction with the whole cell or indeed whole heart, which means that it is difficult to precisely manipulate cells. Additionally, use of

wavelengths with high single-photon interactivity with cells, can lead to unwanted harm, and poor accessibility to deep regions in the tissue is another critical issue to be solved before applying those techniques for future pacemaker technology.

Quite recently, a report used infrared light to affect the beating of an embryonic heart, in vivo (Jenkins *et al*., 2010). The use of infrared light is a different regime to affect the heart beat while still utilizing a presumably single-photon interaction. While the precise mechanism is not yet clear, the use of infrared light appears to reversibly modify the membrane condition, causing contraction. This approach may provide a path to optical pacing using single-photon interactions, and will no doubt be followed with interest. Although this chapter is focused on optical methods (including different regimes of interactions), there is another method with the potential for remote and sterile pacing of the intact heart.. Lee *et al*. have proposed the use of ultrasound to entrain the intact heart (Lee *et al*., 2007), and although ultrasound and light have different interactions, if the final result of the interaction is transient heating of ion channels in the cell membrane (Dalecki *et al*., 2004), the ultrasound and infrared single-photon absorption pacemaking methods may be mediated in the same manner.

2.2 Nonlinear, fast and local approach to optical pacing

Although most of the above-mentioned work using single-photon interactions was not specifically targeted towards pacemakers, it shows the interactions that can be used to modify heart muscle cells or a whole heart. In doing so, we can turn to a different optical interaction which can target specific parts of cells and can be used to trigger biophysical effects in the cells that can be applied to pacemaking. In nonlinear light technology, visible or near infrared (NIR) light can effectively and locally interact with tissues via multiphoton absorption process (Vogel & Venugopalan, 2003). When the photon density is sufficiently high and the resonant molecular absorption energy corresponds to a multiple of photon energy, a number of photons are simultaneously absorbed by single molecule. Tissues contain a large number of UV or near UV absorbing chromophores, such as DNA, proteins, and even water, therefore several photons absorption can occur in the tissues if the incident light has the right wavelength and sufficient intensity. As well as the two-photon absorption, as Vogel *et al.* have shown, more complicated nonlinear absorption processes, such as inverse Bremsstrahlung absorption, leads to avalanche ionization of water and biomolecules (Vogel *et al*., 2005).

Nonlinear absorption can occur in the tissues by high photon density irradiation. Currently established ultrashort pulse laser technology allows us to easily achieve high photon density conditions. Ultrashort pulses have an almost instantaneous (several hundred femtosecond duration) rise in intensity, followed by a period of no irradiation that is, relatively, much longer at a duration of tens of nanoseconds. This, together with tight focusing by suitable objective lenses results in instantaneous high photon density in a local volume. Because the volume of high photon density is limited to the tightly-focused space, the multiphoton absorption occurs only in the sub-femtolitre volume. When NIR light, which can generally pass through biological tissues, is used, the total modification volume is limited to femtolitre scale (Heisterkamp *et al*., 2005; Niioka *et al*., 2008; Shen *et al*., 2005).

Multiphoton absorption by biological tissues is employed to manipulate biological functions, such as inter-/intra-cellular calcium ion waves (Iwanaga *et al*., 2006b; Smith *et al*., 2001), and electrical activities, such as hyperpolarization, depolarization, firing action

potential (Ando *et al*., 2009; Hirase *et al*., 2002; Daria *et al*., 2009), in different types of living cells, including neurons.

These studies used NIR light pulse trains with ~76 or 82 MHz repetition rate, ~100 femtosecond duration, and up to 70 mW in average power. When the cytoplasm is exposed to the tightly focused light for a short time, intracellular calcium ion concentration was increased (Iwanaga *et al*., 2006b; Smith *et al*., 2001). Figure 1 shows calcium-indicator fluorescence images of HeLa cells before (a), just after (b), and following (c-f) exposed to an ultrashort pulse trains for 8 ms. The exposure time was controlled by a mechanical shutter. The cells are stained with fluorescent dye, fluo-4/AM, plasma membrane permeable free calcium ion indicator. The fluorescence intensity, indicating relative calcium ion concentration in the cell, increases with time after the irradiation. Similar, but faster, calcium ion activity evoked by femtosecond laser irradiation was reported in nerve cells (Smith *et al*., 2005) and astrocytes (Zhao *et al*., 2009)

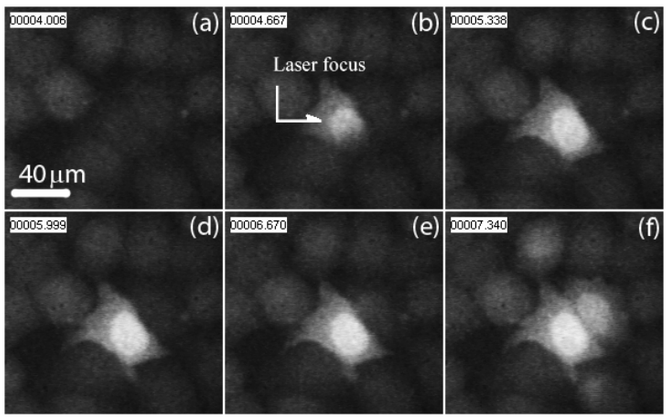

Fig. 1. Calcium indicator fluorescence images of HeLa cells (a) before, (b) just after, and (c-f) over the next two seconds after exposure to 8 ms NIR pulse trains. The time in seconds is noted in each frame. The calcium ion concentration rise is observed in the targeted cell. The laser was focused in the intracellular space outside of the nucleus.

The underlying mechanism of intracellular calcium ion concentration rise was studied (Iwanaga *et al*., 2005; Iwanaga *et al*., 2006a). Calcium ion stores such as endoplasmic reticulum (ER) and mitochondria play a central role in the phenomena. They are distributed in the cytoplasm, particularly near the nucleus. In the normal (non-irradiated) situation, the ER plays a role of regulating the intracellular calcium ion concentration by pumping into the ER or by releasing calcium ions via ion channels into the cytoplasm. To rapidly regulate calcium ion dynamics, the so-called calcium-induced calcium release process occurs, where released calcium ions stimulate further calcium release from ER via ligand activation calcium ion channel receptors in the ER. When the cell is irradiated, light can both directly and indirectly interact with ER and mitochondria. Indirect interaction can be mediated by multiphoton absorption, causing generation of reactive oxygen species in a localized area, where they can modify membrane permeability to release calcium ions to the cytosol. This light-induced calcium release provides the initial trigger for calcium-induced calcium release by the ER.

Under the same laser irradiation conditions, Hirase *et al*. and Ando *et al*. observed activation of electrical activities of (excitable) nerve cells (Hirase *et al*., 2002) and (non-excitable) HeLa

cells (Ando *et al*., 2009). Among these studies, Ando *et al*. studied the relationship between intracellular calcium and electrical behaviors by simultaneously probing calcium ion concentration by fluo-4 and membrane potential by the patch clamp technique. The cell responses to near NIR light exposure are different depending on the irradiation position. When the cytoplasm was exposed to femtosecond light pulses, the membrane was rapidly hyperpolarized and then gradually recovered, consistent with the intracellular calcium ion concentration manner. This is shown in figure 2. The calcium induction by laser irradiation seems to trigger calcium-sensitive potassium ion channels in the plasma membrane, causing the hyperpolarization. When the membrane is irradiated, membrane depolarization (where the membrane potential goes to 0 mV) occurs almost instantaneously, consistent with a very rapid change in permeability (i.e. microablation) of the plasma membrane. However, the depolarization was in some cases followed by unstable repolarization of the membrane potential or in some cases restoration of the membrane potential failed to occur. Regarding the calcium dynamics, when the membrane potential did not recover after irradiation, the calcium concentration also showed incomplete recovery and did not return to pre-irradiation levels. These results indicate that the membrane irradiation can cause a hole in the plasma membrane, which may or may not be recoverable.

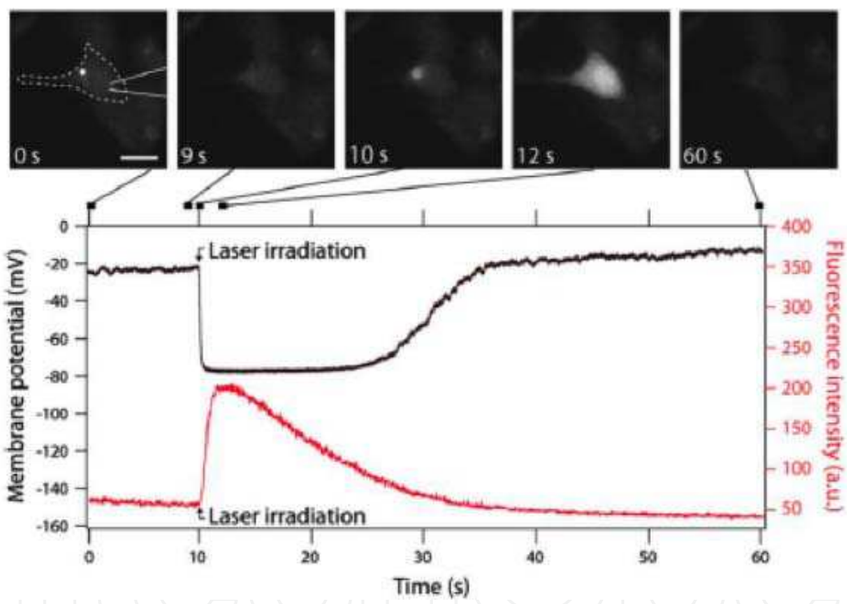

Fig. 2. Calcium indicator fluorescence images of HeLa cells before (a,b), during (c), and after (c-e) exposure to NIR femtosecond pulse trains for 8 ms, and temporal evolution of the intracellular calcium ion concentration and membrane potential of the irradiated cell. The laser was focused in the intracellular space outside of the nucleus. The glass micro-pipette was attached to the membrane of targeted cell in the whole-cell patch configuration. (Reprinted with permission from Ando *et al*., 2009).

It is important to note the effect of femtosecond laser irradiation on cell viability and photodamage. According to the research described above, very few of the irradiated cells were killed when the laser power is carefully tuned and cytoplasm region was irradiated (Iwanaga *et al*., 2006b), while high power or membrane irradiation resulted in low viability or abnormal electrical activity. So long as membrane functionality was not collapsed, the

multiphoton interaction based manipulation can be used, with high spatial selectivity to control cell dynamics, without necessarily causing damage to the cells, and without any interaction at all with regions outside the focal zone, which is related to the fact that light-tissue interaction is so spatiotemporally limited.

Calcium ion concentration and electrical activity play important roles in the regulation of muscle contraction. Previous work from our group, as well as a report by another group (Koester *et al*., 1999), indicates that the femtosecond laser light can independently provide sufficient stimulus to perturb and possibly control the contraction dynamics of a cardiomyocyte. By applying multiphoton light technology, we have recently demonstrated a femtosecond laser pacemaker for heart muscle cells. The detail will be described in the following section.

3. Light-based pacemaker of muscle cells through multiphoton interaction

3.1 Laser synchronization in single heart muscle cells

Calcium ions play a central role in muscle contractile activity. Calcium ion binding to troponin protein initiates the contraction of actin myosin filaments. According to the sliding filament theory, the calcium ion concentrations regulate the contractile length. In natural physiological conditions, the cytosolic calcium ion concentrations are regulated through calcium-induced calcium release, initiated by a triggering small increase of cytosolic calcium concentrations via calcium uptake from the outside of the cell. The increased calcium in the cytosol is then reduced via uptake by the sarcoplasmic reticulum (SR) and pumping to the outside of the cell via ion channels and ion pumps.

We have recently demonstrated a femtosecond laser pacemaker for heart muscle cells (Smith *et al*., 2008). The neonatal rat ventricular muscle cell cultured for 2~4 days were used. Ventricular muscle cells extracted from neonatal rat spontaneously beat because the cells are not perfectly differentiated and separated from pacemaker parts. The spontaneous beating cultured heart muscle cell is periodically exposed (at 1 Hz) to tightly focused femtosecond pulse trains. The laser power was 25 mW. Each exposure duration was 8 ms. We probed the relative cytosolic calcium ion concentration with fluo-4/AM fluorescent dye as well as measuring the contraction itself for some experiments to confirm that the calcium concentration was correlated with the contraction. Figure 3 shows a calcium fluorescence image of the targeted cell and the temporal change in fluorescence intensity averaged

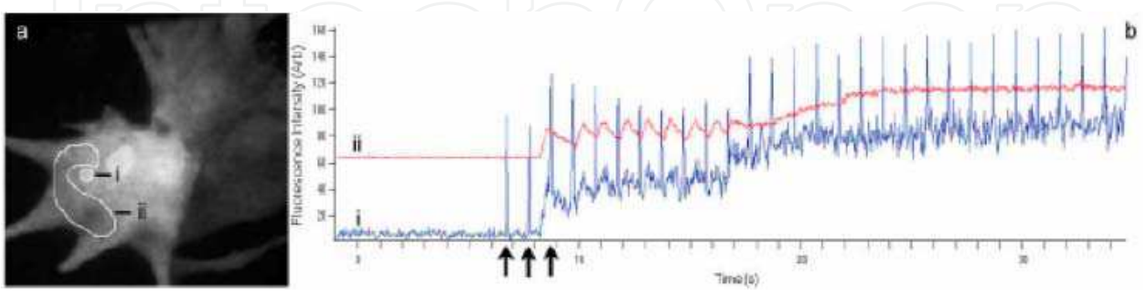

Fig. 3. (a). Heart muscle cell loaded with Fluo-4 calcium indicator. The region 'i' shows the laser focal spot. Region 'ii' encapsulates the surrounding area of the cell. (b) shows fluorescence intensity of region (i) and (ii). The laser is visible as a series of spikes in the fluorescence signal in trace 'i'. The first 3 laser exposures are indicated by vertical allows. (Reprinted from Smith *et al*., 2008. Copyright Optical Society of America).

through the circled cytoplasmic regions. The fluorescence intensity, representing the relative calcium ion concentration in the cytosol, is synchronized with the laser irradiation following 2 exposures to the laser pulse train. We also succeeded in synchronizing the cell with higher (2 Hz) frequency periodic exposure with the same laser irradiation conditions except for the frequency of laser irradiation.

3.2 Laser synchronization in heart muscle cells group

Cultured heart muscle cells undergo spontaneous contractions that depend on substrate properties (Schweitzer & Seliktar, 2007), proximity of surrounding cells (Kaneko *et al*., 2007), as well as other conditions (Vetter *et al*., 1998). Cultured cell samples in our experiments exhibited spontaneous contractions of between 0.2 Hz and 1.5 Hz, depending predominantly on the number and location of surrounding cells.

For target cells with such a pre-existing contraction cycle, periodic laser exposure did not immediately cause the cells to begin contracting with the same periodicity as the irradiation, and the laser pacemaker effect was observed to compete with the spontaneous contraction, where the target cell was entrained by the contraction periodicities of the surrounding cells.

In some cases, however, the laser irradiation could be seen to dominate the contraction periodicities of all cells and act as a pacemaker not only for the target cell but also for the surrounding cells. An example of this is shown in figure 4, where a small group of cells contract in phase with each other, at a rate of approximately 0.2 Hz before laser irradiation. Following periodic 1 Hz laser exposures of 8 ms and 20 mW (shown by trace i), the contractions in all cells begin to synchronize with the exposure periodicity (traces ii-v). The synchronization is clear after the 22nd exposure to laser irradiation, and continues until the laser irradiation is ceased. The calcium level then decreases without cell contraction, for approximately 5 seconds after irradiation is ceased, showing that the laser was driving the contraction of all cells. Finally, spontaneous contraction restarts, with a periodicity that is

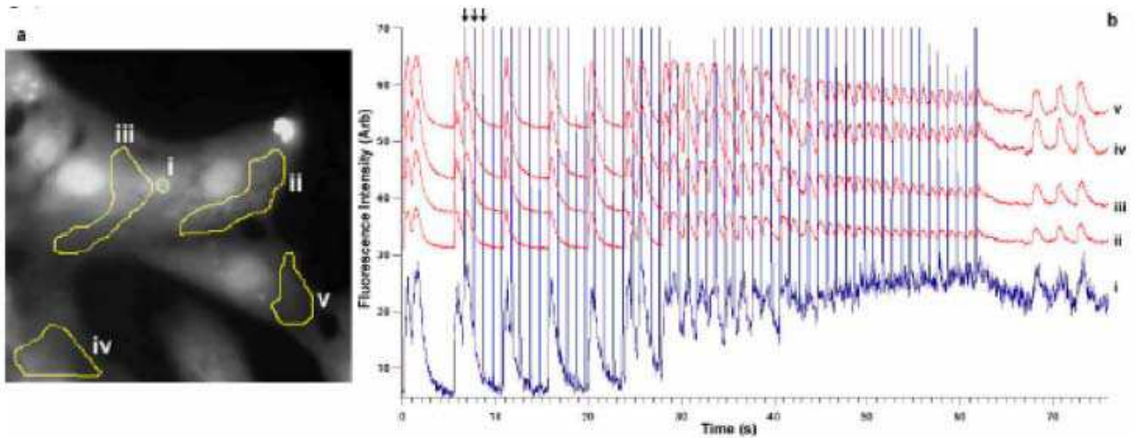

Fig. 4. (a). Heart muscle cells group loaded with Fluo-4 calcium indicator. The group consists of more than 6 cells, spontaneously contracting in synchronization. The region 'i' shows the laser focal spot. Region ii-v encapsulates the cytoplasm area of the target cell and surrounding cells. (b) shows fluorescence intensity of regions i-v. The laser is visible as a series of spikes in the fluorescence signal in trace 'i'. The first 3 laser exposures are indicated by vertical allows. (Reprinted from Smith *et al*., 2008. Copyright Optical Society of America).

unrelated to the periodicities before, and during irradiation. The fluorescence intensity in all cells decreases over several seconds following the final laser exposure before contraction spontaneously restarts, showing that the cells can respond to laser exposure periodicities that are faster than the spontaneous contraction rates for these samples.

3.3 Mechanism of synchronization

The SR may play a central role in the laser-pacemaker effect as does the ER in the calcium ion waves observed in HeLa cells. SR contains a much larger amount of calcium ions compared with the amount present in the cytosol. If the interaction between laser and calcium is the same for cardiomyocytes as it is for non-excitable cells (such as HeLa cells) then the femtosecond laser irradiation causes SR calcium release and activates calcium-induced calcium release in whole cell. One significant difference between cardiomyocytes and non-excitable cell case is the inward calcium current via plasma membrane calcium ion channels. These calcium ion channels can be activated by membrane potential depolarization. As Ando *et al*. reported, light-induced membrane potential change can occur in non-excitable cells. Presumably it also occurs in a similar manner in excitable cells such as cardiomyocytes, although here it is more difficult to measure the light effect since the membrane potential dynamics are fast and complex in excitable cells. Certainly, such effects do occur in neurons (e.g. Hirase *et al*., 2002) and in the case of cardiomyocytes the laser effect on membrane potential depolarization may be also play a role in the laser pacemaking effect. In the report by Ando *et al*., the laser seemed to directly the cell membrane only when the laser focus overlapped the cell membrane. When the laser was focused in the cytoplasm, the membrane potential change seems to result rather from the laser induced change in intracellular calcium, which can itself drastically alter the permeability of the ion channels in the membrane. In short, when the laser was not focused on the cell membrane, the laser had only an indirect effect on the membrane potential.

This implies that the method of synchronization is mediated by calcium release, although we should remember that the direct comparison across cell types is not straightforward, because electrical activity and rates of change in intracellular calcium in muscle cells is more active and dynamic. Regardless, the result showing the synchronization of a group of cells necessarily implies that the cell to cell propagation of the synchronization occurs via action potential generation because laser-induced calcium dynamics of all cells have the same phase. The immediate laser interaction is localized at the laser focus, inside one cell, and the synchronization across groups of cells must then occur via gap-junction or other electrical connection between cells.

Additionally, in contrast to calcium wave generation in non-excitable cells, to evoke the pacemaker effect we need to irradiate a muscle cell repeated times. One single large irradiation could force the cell to raise intracellular calcium and subsequently contract but this method did not provide a means to periodically trigger contraction. Rather, the laser power was reduced and the repeated exposure was observed to entrain the contraction of the target cell as well as neighboring cells.

The accumulation of irradiation may cause a different degree and manner of photodamage. Following irradiation, the minimum level of calcium ion concentration was sometimes observed to increase and the dynamic range of calcium ion concentration during subsequent contraction was reduced. After stopping the laser irradiation, the beating rhythms do not simply return to the conditions before laser manipulation, this may be due to the fact that

the dynamic of the entrained system of cells has been shifted to a different but stable regime, or it may be simply due to the fact that the laser has had a (possibly harmful) effect on the cells. What is clear is that when the laser power was raised further, or the irradiation repeated for a sufficiently long time, the calcium ion concentration in the target cell (but not surrounding cells) became high. There are several possible ways that the laser could harm the cell, the SR permeability may be increased, restricting the uptake of calcium ions, the plasma membrane permeability might be affected, or perhaps the ATP-driven pumping mechanisms are temporarily (or permanently) exhausted. In summary, the laser can affect the cell and overdrive the calcium dynamics. Nevertheless, it is predictable that accumulating photodamage can be minimized if exposure conditions are carefully set. Because the laser focus volume is as small as femtolitre or even less, but the optical pacemaker effect can spread over regions as large as several hundred micrometers in diameter, the photodamage issue can be minimized, possibly by scanning the laser over different targets, and allowing some recovery time for each individual focus region. It may then be possible to apply this technology to clinical and medical applications in the future. It is also worth noting that even a damaging interaction is still a new method with which to modify the normal heart system and study the effects of aberrant contractions around the laser focus on the function of the whole heart. This would require the method to be able to entrain or modify the contraction of cells even when the cells were otherwise entrained by a normal electrical signal as is the case in a normally functioning heart. This point will be discussed further below in Section 3.5.

3.4 Statistic analysis of laser power dependency

We statistically studied the laser power dependency of the femtosecond laser pacemaker phenomena.

In total, over 200 laser-heart muscle cell synchronization trials were performed in the experiments reported here with different laser powers and periodicities. The synchronization of the cell contraction periodicity with the laser exposure periodicity occurred in approximately 25% of all trials for average laser powers of between 15 to 30 mW (measured at the sample) at a laser periodicity of 1 Hz. To quantify the relationship, we restricted the definition of synchronization so that around 5 or more consecutive beats were required to follow the laser periodicity in frequency and phase. With this definition of synchronization, we recorded the results shown in figure 5, over a total of 181 cells using 1 Hz irradiation periodicity. The number of cells were counted that exhibited synchronization and also the number that exhibited some calcium response to the irradiation and/or showed indications of synchronization that did not fit our definition of synchronization as given above. The data necessarily includes experiments from different days, which means that there is a degree of variability in the cell culture conditions. This, as well as the difficulty in achieving large amounts of data where only one parameter is changing, probably accounts for the variation in probabilities across adjacent laser powers.

The data shows that the synchronization generally occurs at the onset of an observable response in the heart muscle cells and shows that while synchronization can be repeatedly induced, more work needs to be done to clarify the precise optical and/or biological parameters that govern the interaction of the cell's spontaneous contraction rate and the external periodicity of the laser influence on the cell dynamics. The data are then further divided into two constituent groups: experiments where a single isolated cell was irradiated,

and experiments where one cell within a group of 2-14 connected cells was targeted and irradiated. While the data is insufficient to conclude the distinction between isolated cells and those within a group, it does point to an interesting possibility; the cell synchronization of an entire group of 2-14 heart muscle cells may be more probable than the synchronization of a single heart muscle cell. More research will be required to determine if this is the case, and this may have implications for the onset of new and often undesirable contraction periodicities in groups of heart muscle cells.

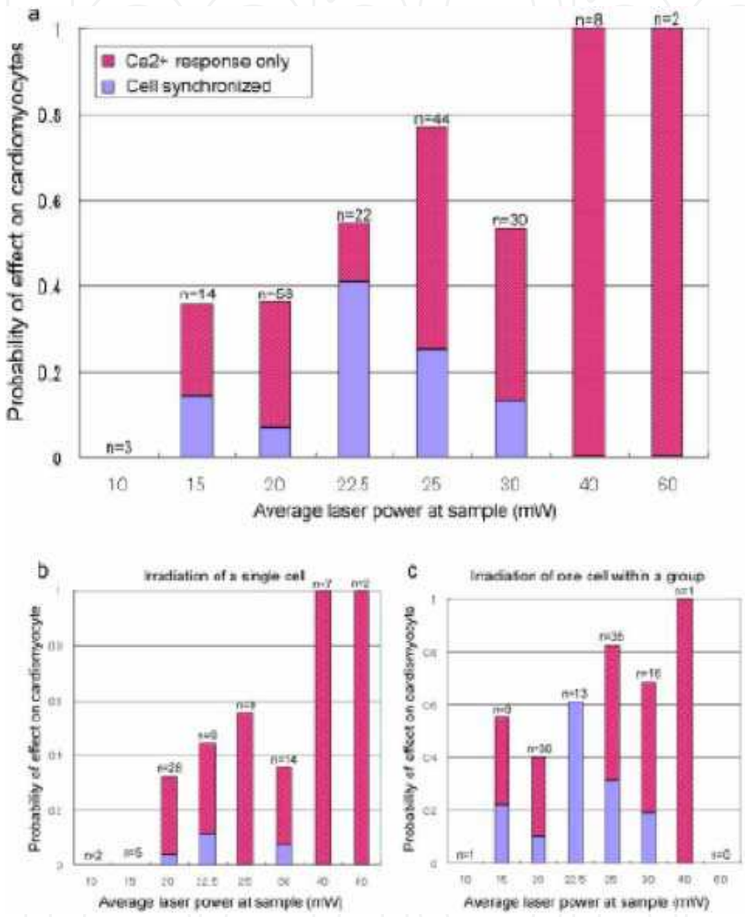

Fig. 5. The probability of generating a synchronized cell response or a calcium response without synchronization. The graph in (a) shows for all data sets of laser irradiation periodicity of 1Hz. In (b), the graph shows the cases where the targeted cell was an isolated heart muscle cell, and (c) shows the cases where the targeted cell was within a group of 2-14 cells. For synchronization to occur in cases shown in (c), all cells in the group were seen to synchronize with the laser periodicity. Conditions necessary to merit the term "synchronization" are described in the main text. (Reprinted from Smith *et al.*, 2008. Copyright Optical Society of America).

3.5 Laser effect on electrically regulated heart muscle cells

When electrical voltage is repeatedly and periodically applied on heart muscle cells, the beating of cells is well-regulated. Optical pacing may become a powerful tool in the study or

treatment of a system of electrically regulated cells, tissues, or organs, due to its ability to perturb existing dynamics in a group of cells or whole heart. We confirmed a perturbation of electrically regulated beating rhythm by transient laser irradiation. Figure 6 shows the temporal change in fluorescence intensity, representing calcium dynamics, of electrically regulated heart muscle cells. The short femtosecond pulse trains of 8 ms duration, represented by a red dashed line, evoked calcium ion concentration increase in the irradiated cell. This result demonstrates that optical pacing can also modify the activity of electrically regulated heart muscle cells. The light-based pacemaker effect can then be stronger than the electrical regulation of the heartbeat. In Figure 6, note that the calcium level in subsequent electrically regulated contractions has a lower peak then the contractions prior to the laser irradiation.

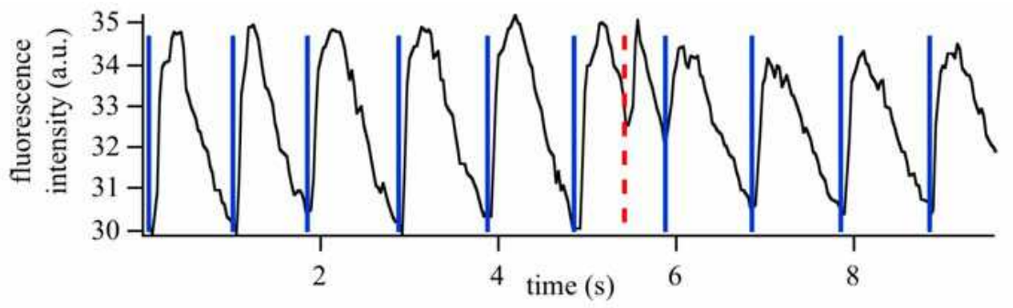

Fig. 6. Fluorescence intensity of an electrically regulated heart muscle cell, which represents the intracellular whole cell calcium concentration. Solid (blue) vertical line shows the timing of electrical stimulation, and dashed (red) line shows the transient laser irradiation, forcing the cell to undergo an abrupt change in contraction dynamics.

3.6 Modeling of the pacemaker effect

In experiments, it is difficult to further study the precise dependence of the optically-controlled activity on the exposure parameters such as the phase and frequency. This is because the spontaneous beating is not perfectly periodic and also because it depends on the individual heart muscle cell conditions, such as rat growth, cell culturing time, and cell density in the dish. Quantifying all of them and their relation to the optical pacing effect requires an extremely large number of experiments using animal-based samples, which is not ideal.

An alternative approach to study the phase and frequency dependency is the use of numerical modeling. We modeled the optically-controlled beating dynamics of heart muscle cells by simultaneous differential equations, based on perturbations to a modified form heart muscle cell model based on the sinoatrial node KYOTO model (Sarai *et al*., 2003). The KYOTO model represents different type of cells (adult rat sinoatrial node) from the one we used in experiments. The reason we chose this model to be modified for modeling laser pacemaker effect is 1) a model of the neonatal rat heart muscle cell is not available because it is not well understood, and 2) the KYOTO model can similarly represent the calcium activity of our specimen, and can exhibit spontaneous oscillation of calcium ion concentration.

The KYOTO model has 50 ordinary differential rate equations for representing intracellular ion concentrations, ion channels dynamics, membrane potentials, and contractile activity.

Without reproducing the large number of equations in full, it is still worth showing some of the essential equations which are most relevant:

$$\frac{d[Na^+]i}{dt} = \frac{-I_{Na\_efflux} - I_{Na\_\inf lux}}{FV} \tag{1}$$

$$\frac{d[K^+]i}{dt} = \frac{-I_{K\_efflux} - I_{K\_influx}}{FV} \tag{2}$$

$$\frac{d[Ca^{2+}]i}{dt} = \frac{-I_{Ca\_efflux} - I_{Ca\_influx} + I_{RyR} - I_{SR\_uptake} + I_{SR\_leak}}{2FV} + \frac{d[Ca^{2+}{}_{buffer}]_{free}}{dt} \tag{3}$$

$$\frac{dV_m}{dt} = \frac{I_{ext} - I_{ion}}{C_m} \tag{4}$$

In the above equations, $[X]_i$ stands for the cytosolic ion concentration of X (X=Na^+, K^+, Ca^{2+}), $[Ca^{2+}{}_{buffer}]_{free}$ for free calcium ion cytosolic concentrations, I_{X_efflux} and I_{X_influx} for inward and outward X currents over plasma membrane, respectively, I_{RyR} for current flows via ryanodine receptors, I_{SR_uptake} for current flow over SR CaATPase, I_{SR_leak} for leak currents via the ryanodine receptor site, V_m for membrane potential, F for the Faraday constant, V for the cell volume, C_m for the plasma membrane capacity, I_{ion} for total membrane ion currents and I_{ext} for the externally applied current.

To model the laser effect, we added a laser term to the calcium ion rate equation:

$$\frac{d[Ca^{2+}]i}{dt} = \frac{-I_{Ca\_efflux} - I_{Ca\_influx} + I_{RyR} - I_{SR\_uptake} + I_{SR\_leak}}{2FV} + \frac{d[Ca^{2+}{}_{buffer}]_{free}}{dt} + \left(\frac{d[Ca^{2+}]}{dt}\right)_{laser} \tag{5}$$

Because the laser effect is localized and must behave differently from any other calcium ion flux, the laser-induced calcium term is added separately to the term containing the other combined calcium related factors.

To simulate the laser effect, we chose a Gaussian function over more typical wave forms such as delta and rectangular functions. Experimentally, the femtosecond laser induces a local increase in the intracellular calcium ions, followed by diffusion of those ions in time through the cell via calcium-induced calcium release manner (Smith *et al*., 2001). The KYOTO model does not contain any spatial dimensions. Therefore, a Gaussian function to simulate the rise and then diffusion of the calcium ion concentration may be the best approximation of the actual geometry of calcium trigger for the model.

By carefully setting Gaussian function constants, the model could successfully represent the laser-beating synchronization. Here, the definition of synchronization is that the period of calcium dynamics is within 1% of laser periodicity and that the phase is locked by laser irradiation. Figure 7(a) shows a simulated result of intracellular calcium ion concentration. Laser irradiation was periodically performed at time points 1512 and thereafter at multiples of 353xN (where N = 0,1,2,....,20) ms, as shown by red dotted lines. As is seen in figure 7(b), the period of calcium dynamics was entrained by the of laser irradiation periodicity after the eighth laser irradiation. The modeling result shows the calcium ion dynamics after laser irradiation stops.

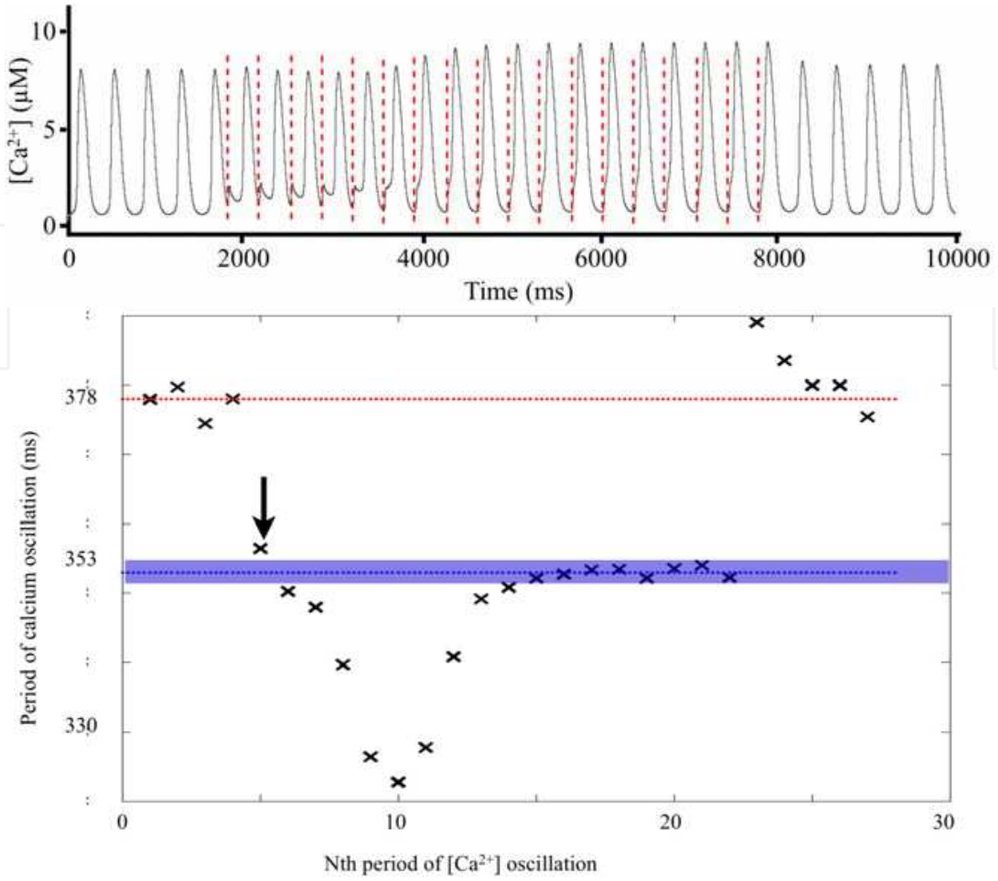

Fig. 7. (a) Simulated intracellular calcium ion concentration modified by 18 periodic exposures to laser irradiation, indicated as dotted vertical lines. (b) shows the evolution of the synchronization, shown as the time interval of the peak in calcium ion concentration. The arrow indicates the period of calcium oscillation just after the first laser irradiation. The blue area in the middle is for the periods of synchronization. After the 11 th irradiation, calcium oscillation is to be synchronized with periodic laser irradiation.

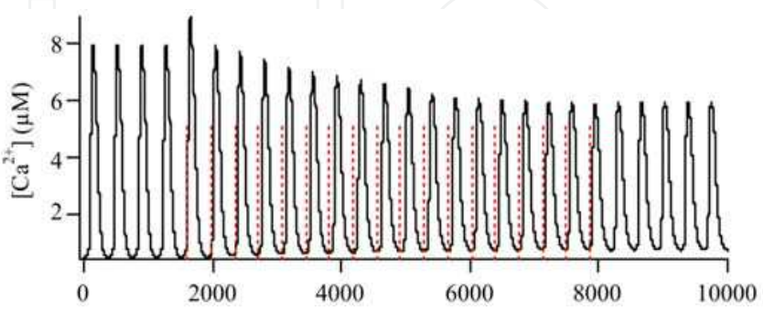

Fig. 8. Intracellular calcium ion concentration model of the heart muscle cell, modified to simulate 18 perioidic exposures to laser irradiation, indicated as dotted vertical lines, when the accumulation effect of SR calcium ion leakage is included in the model.

To better reproduce the empirically observed calcium ion dynamics, we modeled calcium ion leakage from SR, with a slight accumulation effect following repeated exposure,

reflecting possible photodamage. The leakage is represented in the model as another accumulating term in the differential equation for calcium ion. Figure 8 shows the calculated temporal change in intracellular calcium ion concentrations. The oscillation range of the calcium ion concentration gradually becomes small with accumulation of calcium leakage amount. After stopping radiation, the level of calcium ion concentration and its dynamics are not observed to recover. This is very similar to our experimental results, indicating that the calcium ion leakage from SR may really accumulate in our experiments using optical pacing. It is also predictable from the model that either repeating exposures further, or increasing the laser power will cause degradation of the cell activities, as was seen in experiments.

3.7 Model study of the frequency and phase dependency

The modeling approach is useful for a quantitative analysis of the phenomena. The femtosecond laser-induced calcium dynamics were simulated, varying the phase and frequency of the periodic irradiation. The phase is determined to be 0 at the time when $[Ca^{2+}]_i$ is a local maximum. The phase is varied between - 140 and 230 ms, and the frequency ranges over between 298 and 428 ms. In this simulation for investigating frequency and phase parameters, the accumulation of SR calcium ion leakage was excluded due to the overbearing complexity when the number of variables is too high.

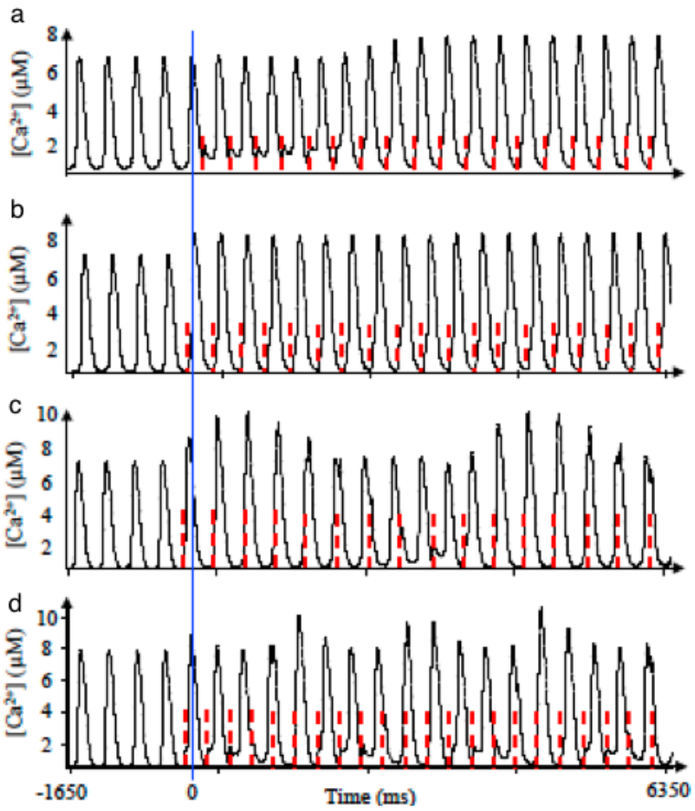

Fig. 9. Simulated intracellular calcium ion concentration modified with modeled periodic laser irradiation, indicated as dotted vertical lines. The dashed vertical line indicates the benchmark of phase of periodic laser irradiation. (a) "delayed synchronization," (b) "complete synchronization," (c) "partial synchronization," and (d) no synchronization.

By simulating the laser-induced calcium dynamics, 4 types of calcium dynamics are obtained. Figure 9 shows 3 types of synchronization (delayed synchronization, complete synchronization, and partial synchronization), as well as the case where no synchronization occured. In delayed synchronization, the synchronization takes time to start. In complete synchronization, increases in cytoplasmic calcium ion required for cell contraction follows all laser irradiation. In partial synchronization, calcium fluctuation partially synchronizes with laser irradiation.

The phase and frequency dependency of the laser pacemaker effect can be visualized in a synchronization map, giving a clue to the dependency on the choice of frequency and starting time for optical pacing experiments While the comparison between the model and experiment is not without complications, the resulting calculated phase and frequency synchronization map do show that there is a strong dependence on both phase and frequency. The strong correlation among the parameters is shown in figure 10.

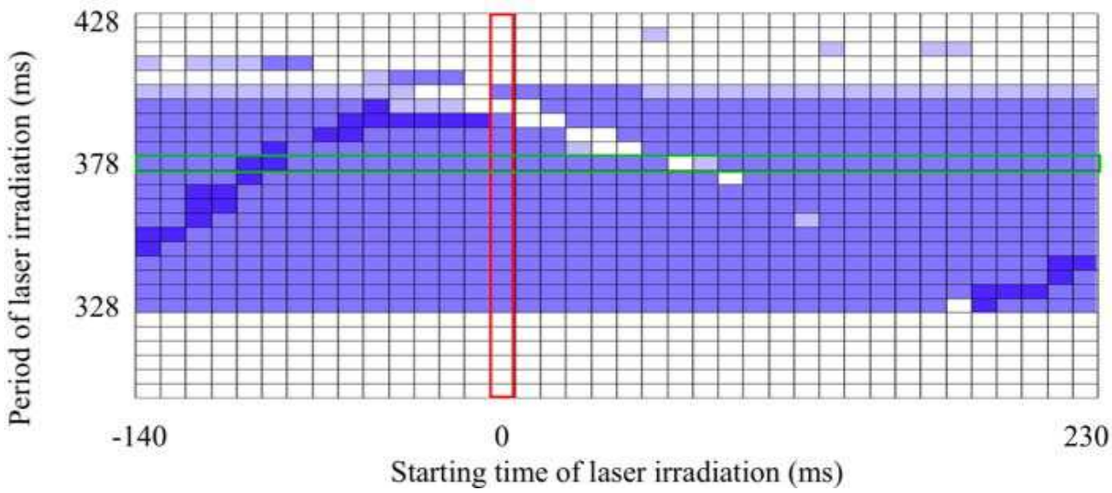

Fig. 10. A map visualizing a relationship between the effect of laser irradiation and both frequency and phase of laser irradiation. The red column outline indicates the baseline for the phase of laser irradiation (0 ms). The green row outline indicates the period of spontaneous calcium oscillation in the model that would occur if there were no laser irradiation. Each color in the map, dark-blue, blue, light-blue, and white, corresponds to 'complete ', 'delayed', and 'partial' synchronization, and no synchronization, that are represented in figure 9. The model shows that even for the choice of laser periodicity which completely matches the spontaneous beat rate, the laser phase should be chosen such that the laser irradiation comes before the peak of the calcium during the contraction process.

In the model, the synchronization only occurs for a restricted range of periodic laser frequency. This was predictable, but it is interesting to quantitatively discuss this result. The region of synchronization spreads from the natural beating frequency. However the distribution of synchronization is different between the upper and lower of natural beating period, the distribution of synchronization in the upper region is less than that in the lower region. This follows from the fact that for longer period laser irradiation, the self-excitation of the cell stimulates the calcium fluctuation before laser irradiation can trigger the cell. The effect is derived from the cardiac refractory stage where action potentials are not generated in order to maintain cellular homeostasis.

The complete synchronization is sensitive to both the phase and frequency, which is related to the refractory stage and the strength of the first laser-induced calcium release. When the first laser irradiation was administered during the cardiac refractory stage, the calcium concentration does not increase sufficiently to cause contraction. Furthermore, when the first laser induced calcium increase causes the intracellular calcium level to rise higher than it does during spontaneous contraction, the refractory stage duration becomes elongated.
Even within the frequency range of synchronization, at some phases, the modeled cell is not synchronized with laser irradiation. When both the period of laser irradiation was close to those of natural calcium oscillation and the starting time of laser irradiation was just after contraction, rhythm of [Ca^{2+}] oscillation did not correspond with rhythm of laser irradiation. These results could be understood from the refractory property of heart muscle cells excitation. However it is interesting that the critical laser irradiation period and starting time are related.
The synchronization map shows interesting interdependencies as well as providing information about which periodicities and starting times are suitable for synchronization. If the simulation times are longer than 10,000 ms, the shape of the map will change. However, since if the goal is synchronization for optical pacing, then the optical parameters of most interest will result in synchronization in less than 10,000 ms so that the current map is already useful. A more serious issue which should be considered is the discrepancy between the spontaneous beat frequency in the model and that observed in typical experiments using cultured cardiomyotyces. Other limitations of the model exist and are discussed below. The current model does not contain spatial dimensions The laser effect must be varied depending on the irradiation position and laser-induced calcium behavior in space is important in the pacemaker effect. Alternative models do exist but we selected the above model for its established performance in at least reproducing known and complex calcium behaviour in cardiomyocytes. The model does not contain parameters regarding surrounding conditions such as substrate type and whether groups of cells or single cells are present, and the type of cell represented in the model is slightly different from the one we used in the experiments.
Nevertheless, the current results already provide information about how to optimize optical pacing. A good starting point suggested from the simulations would be to use the minimum laser power necessary to cause an observable change, to use a frequency slightly higher than the spontaneous beat frequency, and to start the laser irradiation approximately 90 degrees out of phase, and before the calcium concentration peak during spontaneous contraction.

3.8 Perspective for femtosecond laser pacemaker

The laser-induced calcium based technique is unique because of 3-dimensional location-selectivity of the interaction without invasive interactions with surrounding areas. Near infrared light is only marginally absorbed via single photon processes in biological tissues, because there are very few chromophores absorbing NIR light in biological tissues. NIR pulses can only interact with tissues at the tightly focused volume, which is of femtolitre scale, via the multiphoton absorption process. Other orthodox techniques such as electrical, pharmaceutical, and mechanical technique, cannot access deep inside the tissue without interacting with surroundings of a targeted area. While optical technology is not yet ready to replace existing techniques it may develop into a clinical method in the future. In the short-term future it is already well-placed to provide a tool to control and study the contraction of cardiomyocytes.

Recent studies also show femtosecond-laser-induced contraction of smooth muscle cells (Choi *et al*., 2010) and whole live body (Santos *et al*., 2010). These researches support the potential of femtosecond-laser-based optical pacing in different types of muscle cells and in vivo and in situ conditions.

The technique is powerful also because exposure duration and phase can be easily and precisely regulated. A simple mechanical shutter can easily select periodicity and phase of the irradiation.

In the future, femtosecond laser-based techniques (as well as optical technologies utilizing single photon interactions mentioned above) should continue to be employed to discover new groundbreaking interactions and to be used for effective and efficient regulation of cell contraction. This indicates the techniques will open the possibility for not only developing pacemaker technology but also understandings of basic underlying science in fatal cardiac arrhythmia caused by unexpected local distortion of the beating rhythm.

4. Light technology for powering and monitoring implanted electrical devices

In the previous sections, we reviewed the light technology for pacemaker development using direct light-tissue interactions, i.e. using light as the pacemaker itself. Light technology can also be used to drive implanted medical devices for muscle pacemaker.

Implanted medical devices have several requirements which can be improved with the use of emerging light technology. One of the most important requirements is continuity of the device. Essentially for a pacemaker device, its sudden breakdown can cause fatal arrhythmia in the patient. Second, radio-frequency waves used for communication with the implanted device are subject to interference by nearby instruments with potentially very serious consequences.Implantable devices are expected to be compact, wireless, and free from causing or receiving electromagnetic disturbances due to radio-frequency waves, which most of today's implanted devices rely on for power supply or signal transmission.

Light technology has the potential to improve these issues. In terms of the robustness of the device, light is readily available, and can be used to wirelessly provide power for implanted devices containing a solar cell. Using near-infrared light, which easily penetrates biological tissues including skin, implanted devices deep inside the tissues can be used without the concern of removing them to recharge or replace batteries. Apart from the advantage of high transmission in biological tissue, the near-infrared light falls into a spectral range in which photoelectric cells such as solar cells exhibit a high light to electrical power conversion rate. In addition, light techniques have little chance to interfere with nearby instruments. Finally, light-based devices are typically compact. This is because they can be constructed from very small photo diodes and employ light-emitting diodes as receiver and transmitter.

As an aid to future implantable pacemakers, near-infrared light driven wireless power supplies have already been developed (Goto *et al*., 2001a). The implantable device is composed of photodiodes and driven devices, such as a rechargeable battery and an LED as a transmitter. Photodiodes can drive a device as long as the exposure to near-infrared light is sufficient. In demonstrating the implantable power supply system in an adult rat, the light power sufficient to drive implantable devices increased the skin temperature by only around 2 degrees, which is not large enough to cause significant problems for the skin. This result demonstrates that the power supply technology based on a photodiode array can be used for driving an implanted pacemaker device.

By using the wireless power supply technique, two types of prototype devices were demonstrated. One of them is an optically rechargeable battery (Goto *et al*., 2001a). This device is composed of assembled photodiodes with a rechargeable lithium battery. Lithium batteries are appropriate for implantation due to their compact size (e.g. 25mm in diameter, 3.2mm in thickness) and have sufficiently high voltage (~3V) to driving implanted devices. Figure 11 shows a schematic diagram of the near infrared power supply system. The NIR light emitted from the laser diode is collimated and exposed to the photodiode array embedded under the skin. The photodiode array converts the light energy to electric power and supplies the current to a rechargeable battery, which is connected to an implanted device. If the battery is fully charged it can then be used to drive a typical cardiac pacemaker for 6 months without any recharge. Additionally, more than 6000 charge/discharge cycles can be expected for 0.5 % discharge, which corresponds to operating a 20-μ-A-consuming cardiac pacemaker for 24 h. This means that if the battery is recharged once every day, over 100 years of continuous use of the pacemaker is possible, while the lifetime of conventional pacemaker batteries is within the 5-10 years range. The specifications of battery technology, photodiode efficiency and pacemaker current draw will only improve over time, and optical technology for delivering wireless power to implanted devices is already feasible and should become more attractive in the future.

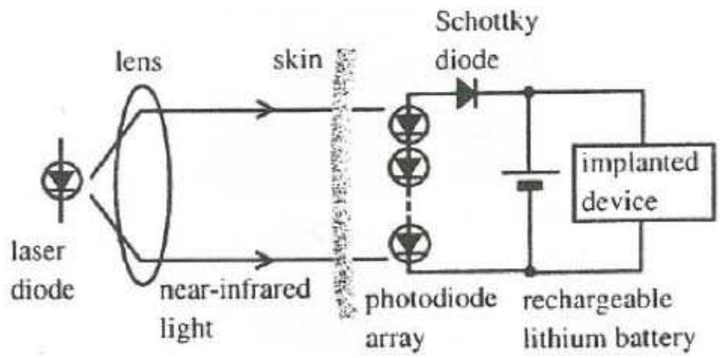

Fig. 11. Schematic diagram of the NIR power supply system. (Reprinted from Goto *et al*., 2001. Copyright IEEE).

The other device we proposed using the power supply technique is transcutaneous telemetry system (Goto *et al*., 2001b). The device uses photodiode arrays for directly driving LEDs used to transmit information to a detector outside the body. Figure 12 shows a schematic diagram of the telemetry system. In this system, an intensity-modulated laser diode is used to drive the photodiode arrays. The photodiode array is then to both drive the LED and for sending a carrier wave to the phase modulator. The carrier wave is phase-modulated by a baseband signal, corresponding to the biological signal. The phase-modulated carrier wave modulates the light emitted from the LED, which is received by external photodiode with lock-in-detection. This technology is unique because power supply and signal transmission is done by only light.

In the published report, the transmitter device is not actually compact since the system requires lenses. Our research group has demonstrated a compact transcutaneous photocoupler-like telemetry system for transmission of biological signals such as directly monitoring electromyograms (Goto *et al*., 2002). In that system, once the LED array is externally driven, the biopotentials can be detected by the receiver. The electronics

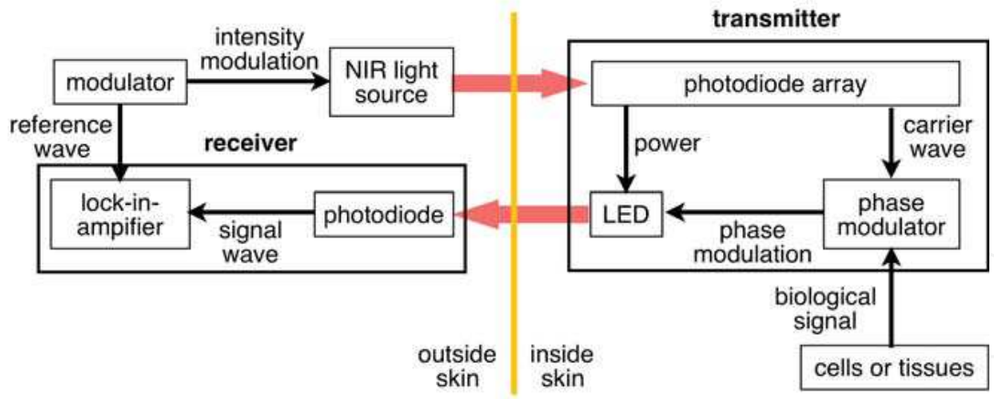

Fig. 12. Block diagram of the all optical telemetry system.

necessary for detecting and amplifying biopotentials can be incorporated into the transmitter. Using this system, biopotentials were obtained from living rats. This compact device is promising for optically recording muscle electrical activities in vivo with safe, wireless, and interference free telemetry.

5. Future perspective

The emerging optical pacemaker technology has the potential to be used as a pacemaker itself, and also to be used to investigate the mechanisms of unwanted arrhythmia and the breakdown of normal contraction conditions. Besides the clinical applications, the light technology can adaptively target new locations inside target tissue, and in the future may possibly even react in real time to counteract the onset of abnormal contraction within the heart. Light-based techniques may not only drive the future development of pacemaker technology but can also help the understanding of the basic underlying science in fatal cardiac arrhythmia caused by unexpected local distortion of the beating rhythm.

This chapter has emphasized femtosecond, localized interactions for studying optical pacing. Other light techniques mentioned in the previous sections based on single-photon light-tissue interactions are not comparable to femtosecond laser irradiations in terms of the speed and localization of the laser-cell interactions and until recently were not advantageous in terms of the invasive nature of using green light which is damaging and non-specifically absorbed throughout the cell. The recent proposal of infrared light-based single-photon optical pacing is also showing promise.

Regardless of the interaction mechanism, the optical pacing results are not only phenomenologically interesting but also attractive for pacemaker technology because of inherent sterility and property of low-interference with other signals or devices. Similarly sterile and interference-free, the use of light for driving and sending a power and telemetry signals to and from implanted-devices has high potential for practical clinical applications. The continuous operation and communication with implantable devices is already achievable.

Most experiments discussed in this chapter have used laser light. The use of LED light or low threshold laser diodes could replace the laser irradiation. As we have shown, implanted LEDs may themselves be driven by externally applied optical irradiation. By combining these concepts with already fully-developed technology, we can conceive of an optically powered, optical pacemaker, running on power by external light or sunlight, driving the

power source for LEDs or tiny laser diodes which generate the pacemaking effect in the heart. These developments in light-based pacemaker technology should drive innovation in general pacemaker technology.

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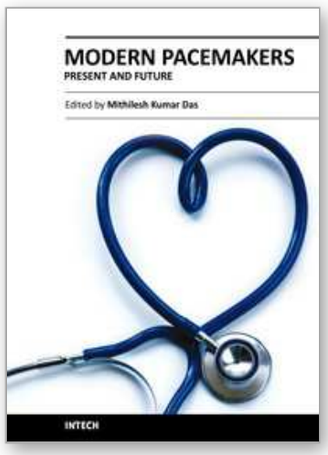

Modern Pacemakers - Present and Future

Edited by Prof. Mithilesh R Das

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The book focuses upon clinical as well as engineering aspects of modern cardiac pacemakers. Modern pacemaker functions, implant techniques, various complications related to implant and complications during follow-up are covered. The issue of interaction between magnetic resonance imaging and pacemakers are well discussed. Chapters are also included discussing the role of pacemakers in congenital and acquired conduction disease. Apart from pacing for bradycardia, the role of pacemakers in cardiac resynchronization therapy has been an important aspect of management of advanced heart failure. The book provides an excellent overview of implantation techniques as well as benefits and limitations of cardiac resynchronization therapy. Pacemaker follow-up with remote monitoring is getting more and more acceptance in clinical practice; therefore, chapters related to various aspects of remote monitoring are also incorporated in the book. The current aspect of cardiac pacemaker physiology and role of cardiac ion channels, as well as the present and future of biopacemakers are included to glimpse into the future management of conductions system diseases. We have also included chapters regarding gut pacemakers as well as pacemaker mechanisms of neural networks. Therefore, the book covers the entire spectrum of modern pacemaker therapy including implant techniques, device related complications, interactions, limitations, and benefits (including the role of pacing role in heart failure), as well as future prospects of cardiac pacing.

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