

# Multi-nodal Nano-actuator Pacemaker for Energy-efficient Stimulation of Cardiomyocytes

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## Abstract

There is continuous interest in maximizing the longevity of implantable pacemakers, which are effective in remedying and managing patients with arrhythmic heart disease. This paper accordingly first proposes miniature actuating nanomachines that inter-connect with individual cardiomyocytes and then deeply explores their energy expenditure when performing basic cardiomyocyte stimulation tasks. Since evoked electrical impulses from a number of actuated cardiomyocytes could coordinate contraction throughout the remaining heart muscle and lead to a heart beat, the miniature actuating nanomachines acting synchronously form a conceptual multi-nodal nano-actuator pacemaker network. Rectangular-, sine-, half-sine-, and sawtooth stimulation pulses with varying configurations are considered for actuation of a single isolated *in-silico* cardiomyocyte by each of the nanomachines. Computer optimization methods with energy consumption as a cost function are utilized to configure preferable sti-

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mulation signals in terms of numbers of stimulation sessions/pulses, pulse amplitudes, and duration. In addition, the simulation data are compared with experimental data obtained using *in-vitro* mouse cardiomyocytes. Among the considered waveforms, half-sine pulses that lead to actuation of a single cardiomyocyte consume minimum energy. None of the used sequences with multiple stimulation pulses reduces the overall energy expenditure of cell stimulation when compared to a single pulse stimulation.

*Keywords:* Nano-actuator, action potential, cardiomyocyte, energy efficiency, pacemaker, stimulation.

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## 1. Introduction

Cardiovascular diseases continue to be a leading cause of morbidity and mortality worldwide [1]. In heart disease affecting the conduction system of the heart, advanced technological solutions have been applied to restore normal heart function [2]. Indeed, pacemaker-therapy is currently an important modality for the management of arrhythmia and certain forms of congestive heart failure. Since the initial success of implantable pacemakers in the 1960s, extensive technological improvements have emerged, making it possible for physicians to restore rhythm disturbances more physiologically. However, existing pacemakers critically suffer from limited battery life. Surgeries needed to replace expired battery cells may impose additional complications for patients.

Current methods to decrease the pacemaker battery consumption focus on designing new techniques and using body energy production. A sensing approach has been designed where information from the implanted stimulation electrode is analyzed and processed to comply with the requirements of particular pacemaker adjustments and optimize energy pacing pulse with an adequate safety margin [3]. In addition, new devices, such as bio-inspired ultra-energy-efficient analog-to-digital converters, micro-scale energy harvesting systems, and solar-powered cardiac pacemakers, have been developed [4], [5], [6], [7]. Furthermore, bio-inspired technology has been designed to use the body energy

21 production, such as heart contraction, blood flow and body movement and tem-  
22 perature (heat) [8].

23 As decreasing the electrode interface potentially decreases the threshold  
24 voltage required for the cardiomyocyte stimulation [9], [10], [11], this imposes  
25 the question whether nanotechnology may lead to novel pacing strategies with  
26 reduced energy consumption relative to the state-of-the-art pacemakers and long  
27 battery lifetime. Of note, the current pacemaker electrodes are large compared  
28 with cardiac cells. The smallest diameter of the pacemaker electrode is about  
29 6 mm – about 60 times the length of a typical cardiomyocyte (approx. 100  
30  $\mu\text{m}$ ) [12], [13].

31 Nanotechnology enables the design and fabrication of nano-scale electrodes  
32 and miniature electronic devices, referred to as nanomachines that can perform  
33 basic sensing, actuation and computing functionalities [14], [15], [16]. If inter-  
34 connected, nanomachines form the concept of nanonetworks with significantly  
35 expanded possibilities [17], [18], [19]. In this study, we introduce the concept of  
36 multiple actuating nanomachines that inter-connect with individual cardiomyo-  
37 cytes, perform basic stimulation tasks by injecting current to the cytosol, and  
38 act synchronously in a form of a multi-nodal **nano-actuator pacemaker net-**  
39 **work** illustrated in Fig. 1. Unlike the conventional pacemakers that stimulate  
40 multiple cardiomyocytes at the tissue level, the nano-actuator pacemaker net-  
41 work stimulates individual cardiomyocytes at the cellular level. The rationale  
42 behind this approach is that evoked electrical impulses/action potentials from  
43 a number of actuated cardiomyocytes could coordinate contraction throughout  
44 the remaining heart muscle owing to conductive gap junctions and, ultimately,  
45 lead to a heart beat.

46 There are many challenges in the design and fabrication of the nano-actuator  
47 pacemaker network. In light of the aforementioned limitations of pacemaker bat-  
48 tery lifetime, we presently examine how the performance of individual nanoma-  
49 chines can be optimized to minimize energy expenditure. This will significantly  
50 define the total energy consumption of the proposed nano-actuator pacemaker  
51 network; a calculation that additionally includes:

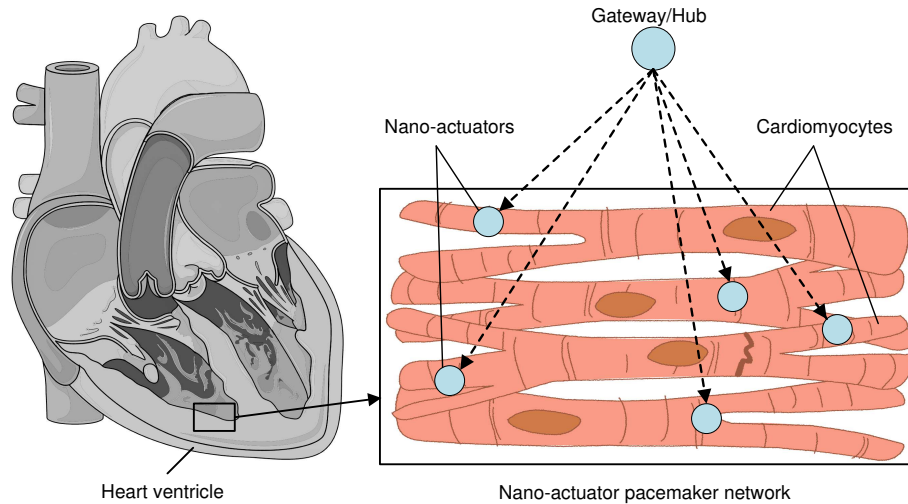


Figure 1: The conceptual multi-nodal nano-actuator pacemaker network with distributed nanomachines interacting with cardiomyocytes. An envisioned paradigm includes nano-actuators placed within the ventricles, with their function coordinated by a gateway/hub (potentially located subcutaneously). This figure was created with an image adapted from Servier Medical Art by Servier. Original images are licensed under a Creative Commons Attribution 3.0 Unported License.

- 52     • the energy required for sensing,
- 53     • the number of (synchronously) actuated cells which is required to generate
- 54         a heartbeat, and
- 55     • the energy used by the gateway/hub.

56     Hence, we consider electrical properties of an isolated *in-silico* cardiomyo-  
 57     cyte to analyze different stimulation pulse characteristics and develop optimized  
 58     energy actuation strategies. First, we apply rectangular-, sine-, half-sine- and  
 59     sawtooth pulses with varying configurations in terms of numbers of stimulation  
 60     sessions, amplitudes, and duration. The optimal strategy for each configuration  
 61     is determined utilizing computer optimization methods with energy consump-  
 62     tion as a cost function. We were particularly interested in the effects of varying  
 63     the number of stimulation sessions, since this has been previously shown to  
 64     decrease action potential threshold in neural axons [20]. Indeed, there are com-

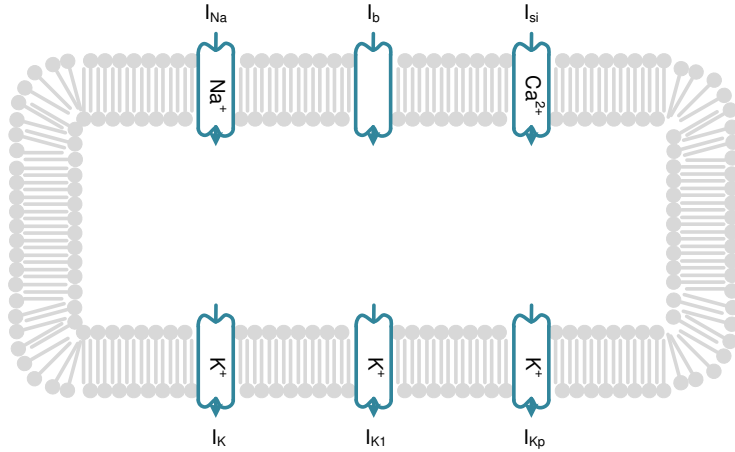


Figure 2: A simple schematic of six current flows across the cardiomyocyte membrane: the fast sodium current  $I_{Na}$ , the slow inward current  $I_{si}$  consisting primarily of calcium ions, the time-dependent potassium current  $I_K$ , the time-independent potassium current  $I_{K1}$ , the plateau potassium current  $I_{Kp}$ , and the background current  $I_b$  [21].

65 plex and non-linear changes of cardiac membrane potentials in the sub-threshold  
 66 region (between the resting potential and the action potential threshold), indi-  
 67 cating changed sensitivity (as illustrated later in Fig. 3(b)). Based on the simu-  
 68 lations, we ultimately compare the data with the experimental data obtained  
 69 when one-, two-, and three rectangular-pulse stimuli with fixed duration and  
 70 inter-pulse intervals were applied to an isolated *in-vitro* cardiomyocyte.

71 The remainder of the paper is organized as follows. Section 2.1 briefly pre-  
 72 sents the computational model that we adopt to analyze the effects of *in-silico*  
 73 cell stimulation with signals closely described in Section 2.2; Section 2.3 and  
 74 Section 2.4 define energy consumption of the considered signals and the opti-  
 75 mization method, respectively, whereas Section 2.5 describes the acquisition of  
 76 experimental data via *in-vitro* cell stimulation. Section 3 presents the results.  
 77 Ultimately, Section 4 concludes the study.

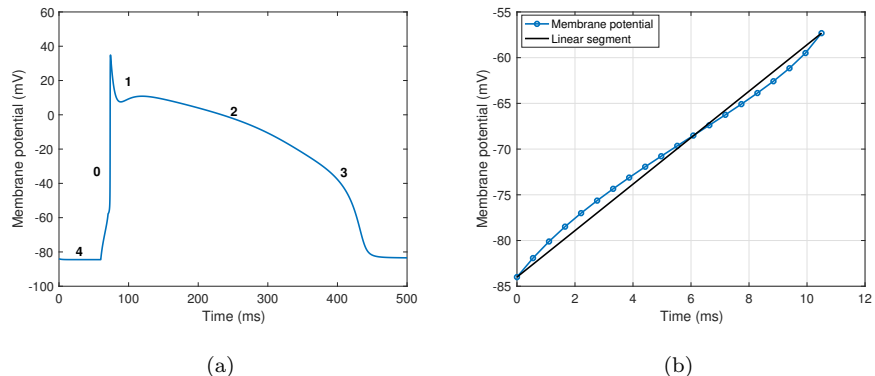


Figure 3: (a) The phases in temporal changes of a ventricular cardiomyocyte action potential: in phase 4, *resting membrane potential*, the inward potassium rectifier maintains the membrane potential. In phase 0, *rapid depolarization*, sodium ions diffuse in the cell and cause rapid upstroke of the membrane potential. In phase 1, *initial repolarization*, the sodium channels and slow outward currents lead to the early depolarization. In phase 2, *plateau phase*, the influx of calcium through the L-type calcium channels and the outward potassium maintain the plateau stage. In phase 3, *repolarization*, sodium, and calcium channels all close and membrane potential returns to resting membrane potential. (b) The non-linear cardiac membrane potential under the stimulation amplitude of  $4.20 \mu\text{A}/\text{cm}^2$  and duration 10.50 ms, indicating changed sensitivity in the sub-threshold region from the resting potential to the action potential threshold.

## 78 2. Methods

### 79 2.1. Cardiomyocyte Model

80 A cardiomyocyte consists of the lipid bilayer membrane punctuated by ion  
81 channels, which produce transmembrane ionic currents, as shown in Fig. 2.  
82 Ionic fluxes triggered by electrical stimulation of the cell membrane alter the  
83 **membrane potential**. When the electrical stimulation is below a certain thresh-  
84 hold so that the membrane potential is not sufficiently depolarized, the cell re-  
85 stores its membrane potential to a resting level (for cardiomyocytes  $\approx -80$  mV).  
86 However, when the depolarization exceeds the threshold potential, the cell un-  
87 dergoes an **action potential**, which comprises a cascade of openings of various  
88 ion channels, transporters, exchangers, and pumps. Fig. 3(a) shows the action

89 potential of a ventricular cardiomyocyte, which is typically subdivided into five  
 90 phases: phase 4, phase 0, phase 1, phase 2, and phase 3.

91 Various models exist in the literature describing action potential generation  
 92 within a single cardiomyocyte [22], [23], [24], [12], [25], [26], or the propagation  
 93 of action potentials through a single or multiple cardiomyocytes [27], [28], [29],  
 94 [30]. Solving these existing models requires numerical methods [31]. Important  
 95 differences between these models include varying descriptions of ionic currents,  
 96 in particular, the sodium current which plays an important role in cell excitation.  
 97 Unlike most of the available single cardiac cell models, the Luo-Rudy model  
 98 (LRd) includes comprehensive analysis of sodium channel function. Therefore,  
 99 we focus on action potential generating mechanisms in an isolated cell based  
 100 on the LRd model and the Hodgkin-Huxley-type formalism of the mammalian  
 101 action potential as [21], [32]:

$$\frac{dV_m(t)}{dt} = -\frac{1}{C_m} [I_{ion}(V_m, t) - I_{stim}(t)], \quad (1)$$

102 where  $V_m(t)$  is the membrane potential,  $C_m$  is the membrane capacitance,  
 103  $I_{ion}(V_m, t)$  is the current produced by the flux of ions, and  $I_{stim}(t)$  is the current  
 104 injected by the nano-actuator. The current  $I_{ion}(V_m, t)$  is defined as:

$$\begin{aligned} I_{ion}(V_m, t) &= I_{Na}(V_m, t) + I_{si}(V_m, t) + I_K(V_m, t) \\ &+ I_{K1}(V_m) + I_{Kp}(V_m) + I_b(V_m), \end{aligned} \quad (2)$$

105 where  $I_{Na}$  is the fast sodium current,  $I_{si}$  is the slow inward current of calcium  
 106 ions,  $I_K$  is the time-dependent potassium current,  $I_{K1}$  is the time-independent  
 107 potassium current,  $I_{Kp}$  is the plateau potassium current, and  $I_b$  is the back-  
 108 ground current (refer to [21] for more details).

109 The change in membrane potential during an applied stimulus is nonlinear.  
 110 As illustrated in Fig. 3(b), in the sub-threshold region, the membrane poten-  
 111 tial first exhibits logarithmic growth before the intersection point with the linear  
 112 function, and thereafter exponential growth following after the intersection point

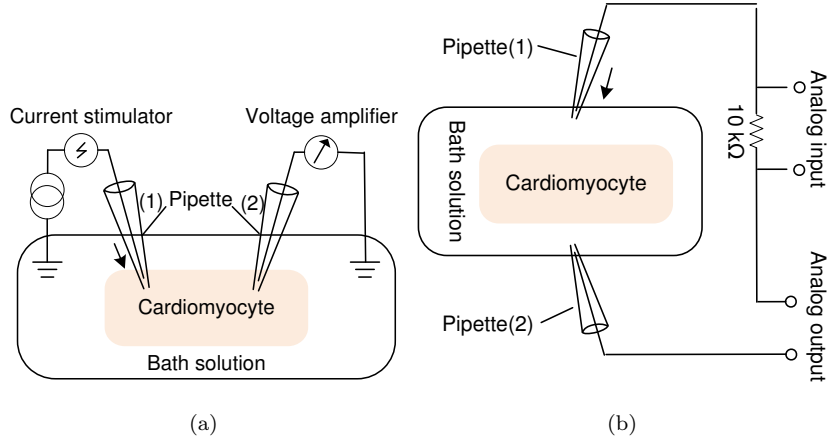


Figure 4: Cardiomyocyte stimulation strategies: (a) Stimulation with direct current injection. The pipette (1) is used to stimulate the cell; the pipette (2) is used to measure the membrane potential. (b) Stimulation with applied electrical field. The pipette tip resistance is  $\approx 2 \text{ M}\Omega$ , distance between pipettes is  $\approx 25 \text{ }\mu\text{m}$ , and cell size  $100 \times 20 \times 20 \text{ }\mu\text{m}$ .

113 with the linearly growing action potential initiation. This has interesting impli-  
 114 cations. For example, at steeply rising parts of this curve, the cardiomyocyte is  
 115 expected to be particularly susceptible to action potential initiation. This furt-  
 116 her motivates us to include consideration of stimulus protocols with multiple  
 117 pulses, which may take advantage of the non-linear nature of membrane voltage  
 118 sensitivity.

## 119 2.2. *In-silico Cell Stimulation*

120 A nano-actuator within the pacemaker nano-network (Fig. 1) stimulates a  
 121 cell by injecting current directly to the cytosol. We use the same stimulation  
 122 strategy, which is depicted in Fig. 4(a), for *in-silico* cell stimulation by injecting  
 123  $I_{stim}$  to the cytosol. This approach contrasts with that employed by present-day  
 124 pacemakers, which stimulate a cardiac tissue by applying electrical field without  
 125 cell puncturing. We use the same, electric field-based stimulation strategy for  
 126 in-vitro cell experiments (Fig. 4(b)), with electrodes placed near the cell in the  
 127 base solution (see further description in Section 2.5).



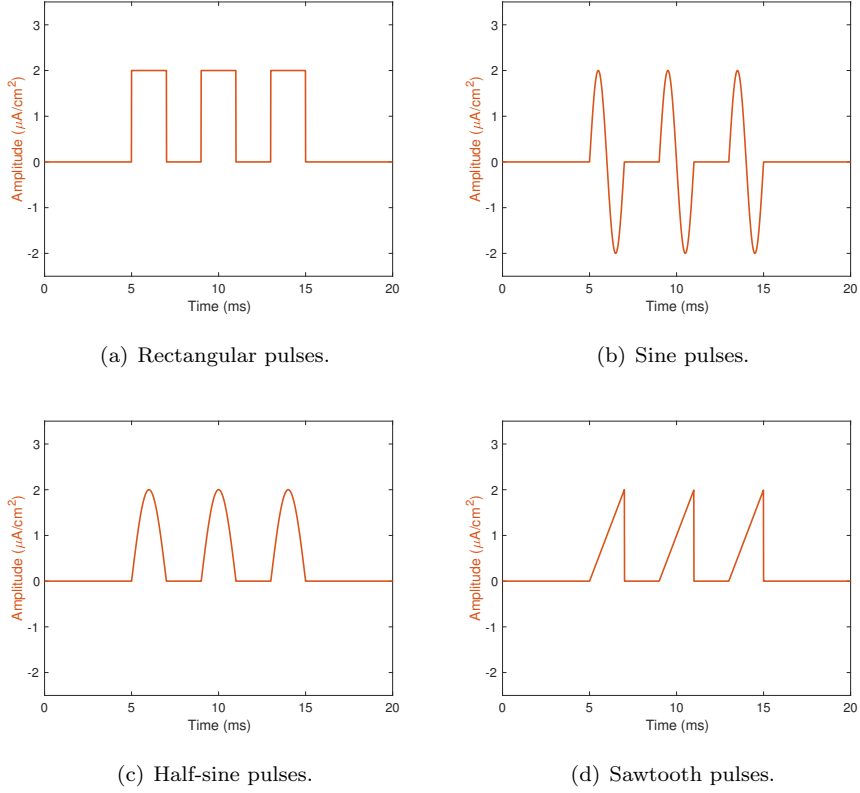


Figure 5: Four three-pulse signals for *in-silico* cell stimulation: all the stimulation pulses start at 5 ms, the stimulation amplitude is  $2 \mu\text{A}/\text{cm}^2$ , and the duration and delay between two consecutive pulses are both 2 ms.

128 To test how different pulses affect the energy consumption of the nano-  
 129 actuator, we compare the excitatory effects of rectangular-, sine-, half-sine-,  
 130 and sawtooth pulses and their influence to the excitation of cardiomyocyte(s)  
 131 in terms of the energy used [33], [34]. Fig. 5 shows four different three-pulse  
 132 stimuli with equal peak amplitudes, duration, and inter-pulse periods. By var-  
 133 ying the number of pulses in the stimulation train ( $n$ ), pulse amplitude ( $A$ ),  
 134 pulse duration ( $t_d$ ), and inter-session intervals/delays ( $\tau$ ), our aim is to optimize  
 135 the stimulation protocol to successfully trigger action potentials with minimal  
 136 energy consumption. Note that better more complex signals possibly exist, e.g.,

137 the action-potential like pulses that we have initially considered in preliminary  
138 analyses. Since, depending on the configuration, the action-potential like pulses  
139 can be considered as similar to half-sine pulses and ramp-like pulses, we exclude  
140 them in the presented analysis. We refer to 1) difficulties in manipulation with  
141 configuration of action-potential like pulses; apart from the amplitude, duration,  
142 and inter-pulse interval that we vary in the presented scenarios, the actual wa-  
143 veform/shape can be also considered as an additional variable in action-potential  
144 like pulses. Thus, we cannot properly compare it with the simpler pulses. We  
145 also refer to 2) the low-pass filter nature of the cellular membrane preventing  
146 all action-potential like pulses to pass the system and show at the output [21].

147 The *rectangular pulse* is commonly used for electrophysiological experiments  
148 in excitable cells. Either bi-phase or mono-phase rectangular pulses are em-  
149 ployed, analytically defined as:

$$I_{sq}(t) = \begin{cases} A, & (N-1)T \leq t < (N-1)T + t_d, \\ 0, & \text{elsewhere,} \end{cases} \quad (3)$$

150 where  $T = t_d + \tau$ ,  $t_d$  is the stimulus duration,  $\tau$  is the delay time between two  
151 pulse stimuli,  $A$  is the stimulation amplitude, and  $N$  is the order of the pulse.

152 The *sine pulse* is also used in electrophysiology [35], [36]. Sine pulses are  
153 defined as:

$$I_s(t) = \begin{cases} A \sin(\omega_1 t), & (N-1)T \leq t < (N-1)T + t_d, \\ 0, & \text{elsewhere,} \end{cases} \quad (4)$$

154 where  $\omega_1$  denotes angular velocity equal to  $2\pi/t_d$ .

155 The (positive) *half-sine pulse* only charges the cell, unlike the sine pulses  
156 which, in addition, discharge the cell. Half-sine pulses are defined as:

$$I_{hs}(t) = \begin{cases} |A \sin(\omega_2 t)|, & (N-1)T \leq t < (N-1)T + t_d, \\ 0, & \text{elsewhere,} \end{cases} \quad (5)$$

157 where  $\omega_2 = \pi/t_d$ .

158 Ultimately, the *sawtooth pulse* ramps upward and then sharply drops. Saw-  
159 tooth pulses are defined as:

$$I_{saw}(t) = \begin{cases} -\frac{A}{\pi} \arctan(\cot(\omega_3 t)) + \frac{A}{2}, & (N-1)T \leq t, \\ & < (N-1)T + t_d \\ 0, & \text{elsewhere,} \end{cases} \quad (6)$$

160 where  $\omega_3 = \pi/t_d$ .

### 161 2.3. Computation of Energy Consumption

162 When actuating a single cardiomyocyte, the energy used for excitation is  
163 given by:

$$E(t_s) = \int_0^{t_s} I_{stim}(t)^2 R dt, \quad (7)$$

164 where  $I_{stim}(t)$  is the injected current of each pulse from the nano-actuator,  
165 defined in (3)-(6),  $R$  is the total resistance between the anode and cathode  
166 of the nano-actuator electrode,  $t_s$  is the total stimulation time, and  $t$  is the  
167 actual time. Thus, decreasing the current injection can reduce the energy of the  
168 nano-actuator and extend the pacemaker longevity.

169 Simulated excitation of a cell is dependent on the amplitude, duration, and  
170 period of the stimulus, and whether the stimuli are applied as a train of pulses.  
171 To successfully generate an action potential, the amplitude of a single-pulse  
172 stimulus needs to be sufficient to initiate the sodium influx. We additionally  
173 test the usage of multiple-pulse signals with different (lower) amplitudes to  
174 exploit ion channel dynamics (explained in Section 2.1). Given that the square  
175 pulse signal is defined with (3), we calculate the energy of the multiple-pulse  
176 square signal as:

$$E_{sq}(t_s) = \int_0^{t_s} I_{sq}(t)^2 R dt \quad (8)$$

177 where  $t_s = nt_d + (n - 1)\tau$  is the total stimulation time, and  $n$  is the number  
 178 of stimulation sessions. Similarly, by combining (4), (5) and (6) with (7), we  
 179 calculate the energy of the multiple-pulse sine-, half-sine-, and sawtooth signals,  
 180 respectively, as:

$$E_s(t_s) = \int_0^{t_s} I_s(t)^2 R dt, \quad (9)$$

$$E_{hs}(t_s) = \int_0^{t_s} I_{hs}(t)^2 R dt, \quad (10)$$

$$E_{saw}(t_s) = \int_0^{t_s} I_{saw}(t)^2 R dt, \quad (11)$$

181 where  $t_s = nt_d + (n - 1)\tau$  is the total stimulation time.

#### 182 *2.4. Computer Optimization*

183 According to (7), the energy consumption is square proportional to the sti-  
 184 mulation amplitude and linearly proportional to the number of stimulation pul-  
 185 ses and stimulation duration. We are however unable to derive an analytical  
 186 solution for the optimized characterization of the stimulation due to the com-  
 187 plexity of the underlying LRd model. We therefore resort to computer opti-  
 188 mization methods to find the optimized combination of the pulse number ( $n$ ),  
 189 amplitude ( $A$ ), duration ( $t_d$ ), and inter-session intervals ( $\tau$ ) which minimizes  
 190 energy usage.

191 MATLAB 2018b provides the powerful global optimization toolbox with a  
 192 variety of optimization methods to solve global optimization problems. Table 1  
 193 compares seven optimization methods. First, we eliminate all methods/solvers  
 194 that require setting initial values (Global Search, MultiStart, Pattern search).  
 195 In addition, particle swarm and genetic algorithms both consume significant  
 196 computer resources, whereas simulated annealing finds a global value but often  
 197 offers non-optimal results. The surrogate algorithm from the global optimi-  
 198 zation toolbox, however, approximates an objective function and balances the  
 199 optimization process between two goals: exploration and speed. Furthermore,  
 200 the surrogate algorithm can find a global minimum of an objective function

201 using few objective function evaluations and the boundary condition of the pa-  
 202 rameter. Therefore, we choose the surrogate algorithm in this study to find the  
 203 optimal configurations of stimulation pulses for cardiomyocytes in terms of the  
 204 energy they use.

Table 1: Comparison of different optimization methods.

Solvers	Convergence	Initial Point	Methods	Need bound constraints	Run in parallel
Global Search	Local optimum	Stochastic	Gradient-based	-	-
MultiStart	Local optimum	Stochastic deterministic combination	Gradient-based	-	Yes
Pattern search	Local optimum	User-supplied	No gradients	-	Yes
Surrogate	Global optimum	Automatic	No gradients	Yes	Yes
Particle swarm	No convergence proof	Automatic	Population-based	Yes	Yes
Genetic Algorithm	No convergence proof	Automatic	Population-based	-	Yes
Simulated Annealing	Global optimum	Automatic	-	Yes	Yes

\* not specified

205 The general form of the algorithm is  $[x, fval] = \text{surrogateopt}(fun, lb, ub,$   
 206  $options)$ , where  $x$  is the optimized parameter,  $fval$  is the optimal value of  
 207 the objective function,  $fun$  is the objective function,  $lb$  is the lower bound  
 208 of the parameters being optimized,  $ub$  is the upper bound of the parame-  
 209 ters, and  $option$  is the modifier of the search procedure. For  $option$ , we set  
 210  $MaxFunctionEvaluations = 360$  and  $MinSampleDistance = 10^{-6}$ . In the  
 211 cost function, we use  $ode45$  function to solve ordinary differential equations with  
 212 variable input (different stimulation). The time step of solving the ordinary dif-  
 213 ferential equation function is 0.001 ms, and its tolerance is  $10^{-3}$ .

## 214 2.5. In-Vitro Cell Stimulation

215 For the experiments, we used isolated mouse ventricular cardiomyocytes that  
 216 were loaded with 1  $\mu\text{M}$  calcium-sensitive dye (Fluo-4AM, Invitrogen). Cells were  
 217 placed under a microscope (Eclipse Ti-U, Nikon) in an imaging chamber (RC-  
 218 49FS, Warner), containing an extracellular solution with a composition of 150

219 mM NaCl, 5.4 mM KCl, 0.33 mM NaH<sub>2</sub>PO<sub>4</sub>, 1 mM MgCl<sub>2</sub>, 1.13 mM CaCl<sub>2</sub>,  
220 10 mM glucose, and 10 mM HEPES (ph adjusted to 7.4 with NaOH). The  
221 conductance of the extracellular solution was  $\approx 20 \mu\text{S}/\text{cm}$ .

222 The two patch pipettes were placed on either side of a single cardiomyocyte,  
223 as illustrated in Fig. 4(b), and connected to an analog output of a data acqui-  
224 sition board (NI PCIe-6353 National Instruments) for cell stimulation. The  
225 cardiomyocyte was stimulated by passing current between the pipettes in accor-  
226 dance with the applied voltage at 1 Hz using 1, 2 or 3 consecutive rectangular  
227 pulses with the duration and the interpulse interval fixed to 5 ms. The pulse  
228 amplitude was varied during the experiment from 1-10 V in 1 V increments.  
229 To determine the voltage threshold for cell activation, the fluorescence of the  
230 calcium-sensitive dye was recorded.

231 The current injected is anticipated to flow both through and around the cell,  
232 similar to a pacemaker immersed in the myocardium. However, we expected  
233 that the part of the current inducing activation was proportionally changed in  
234 accordance with the applied voltage.

### 235 3. Results

#### 236 3.1. Simulation Results

237 We first adopted three protocols shown in Table 2 by varying only the ampli-  
238 tudes and number of pulses to characterize the square-, sine-, half-sine-, and sa-  
239 wtooth pulses used to stimulate an isolated *in-silico* cardiomyocyte. Visualized  
240 cellular responses in Fig. 6 illustrate that, depending on the pulse characteris-  
241 tics, multiple-pulse stimuli can lead to successful initiation of action potentials.

242 We then applied the surrogate algorithm ranging the relevant signal char-  
243 acterization parameters as follows:  $n \in \{1, 2, 3, 4, 5\}$ ,  $A = (0, 60] \mu\text{A}/\text{cm}^2$ ,  
244  $t_d = [0.10, 30]$  ms, and  $\tau = [0.10, 10]$  ms, and assumed the normalized cell  
245 resistance,  $R = 1 \Omega\text{cm}^2$ . The optimization method was easily stuck in the  
246 local minimum since the objection function was nonlinear. The simulation  
247 was run a hundred times for each protocol. For each optimization, we set the

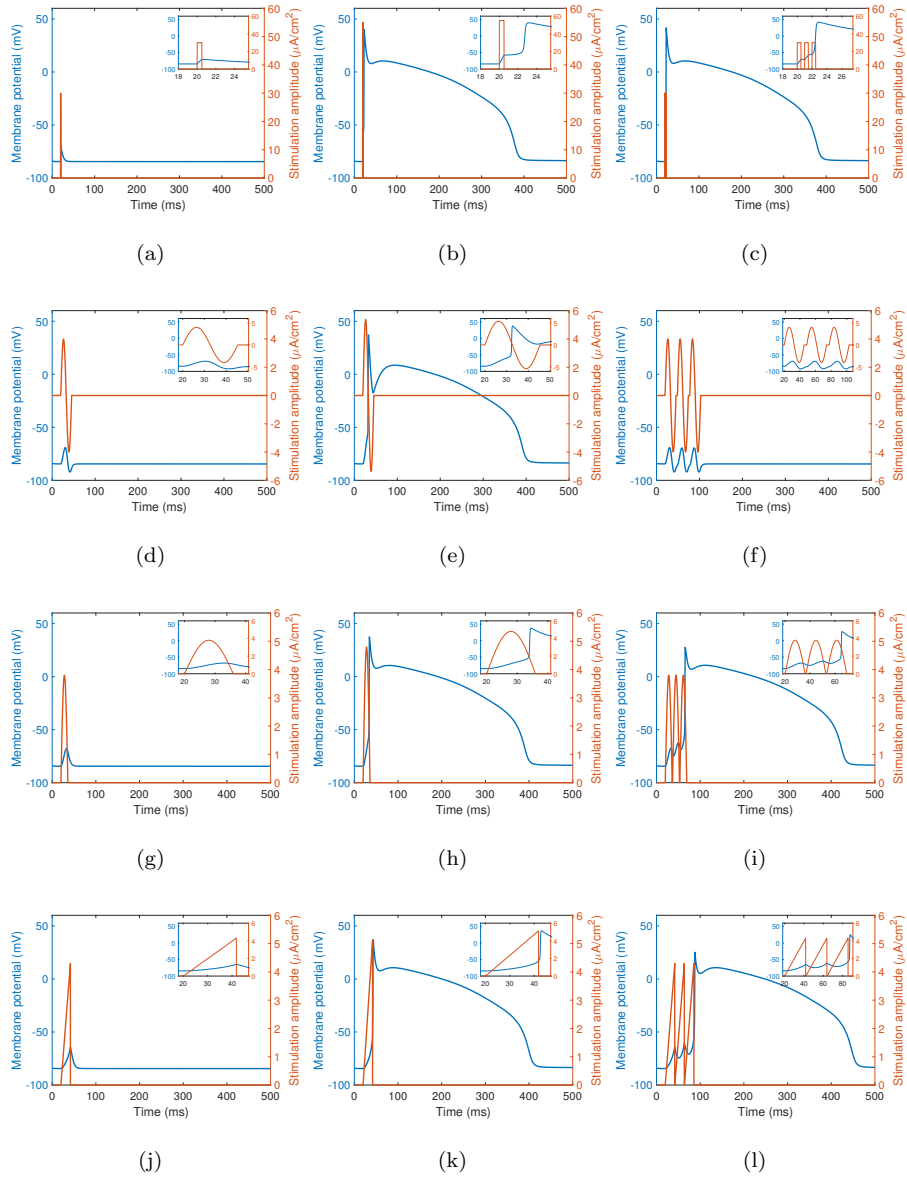


Figure 6: The non-optimized stimuli configurations from Table 2 applied to the *in-silico* cardiomyocyte: (a-c) rectangular pulse(s); (d-f) sine pulse(s); (g-i) half-sine pulse(s); (j-l) sawtooth pulse(s).

Table 2: Non-optimized stimuli configurations used to generate cellular responses in Fig. 5(a)-5(l).

Pulse shape	Pulse(s)	$A$ [ $\mu\text{A}/\text{cm}^2$ ]	$t_d$ [ms]	$\tau$ [ms]
Rectangular	1	30.00	0.50	-
	1	55.00	0.50	-
	3	30.00	0.50	0.50
Sine	1	4.00	25.36	-
	1	5.37	25.36	-
	3	4.00	25.36	3.39
Half sine	1	3.80	15.94	-
	1	4.80	15.94	-
	3	3.80	15.94	0.76
Sawtooth	1	4.30	21.75	-
	1	5.12	21.75	-
	3	4.30	21.75	0.20

248  $MaxFunctionEvaluations = 360$  and  $MinSampleDistance = 10^{-6}$ . The op-  
249 timized parameters of one-, two- and three-pulse stimuli are shown in Table 3,  
250 and the optimized energy consumption in Fig. 8 as a function of the number  
251 of the stimulation pulses. From the obtained output of the optimization met-  
252 hod, we infer that the single-pulse stimulation configurations perform better  
253 in terms of the energy relative to the multiple-pulse stimulation. This impro-  
254 ved performance occurs despite the non-linearity of membrane voltage changes  
255 during the stimulation period, which suggested that multiple-pulse stimulation  
256 might have been a better candidate (as explained in Section 2.1). We also in-  
257 fer that a half-sine one-pulse stimulation outperforms other waveforms. Fig. 7  
258 shows the membrane potentials as responses to the stimulation characterized  
259 according to Table 3. Specific scenarios are depicted in Fig. 7(e) and Fig. 7(f)  
260 where the cell is over-stimulated by repetitive sine pulses. This was expected as  
261 negative half-periods of the sine pulse repolarized the cellular membrane after  
262 being depolarized by positive half-periods.

263 The preference for the half-sine- and rectangular pulses presumably origi-  
264 nates from the low-pass filter nature of the cellular membrane [21], as well as  
265 apparent differences in magnitudes of the Fourier transforms of the signals, as



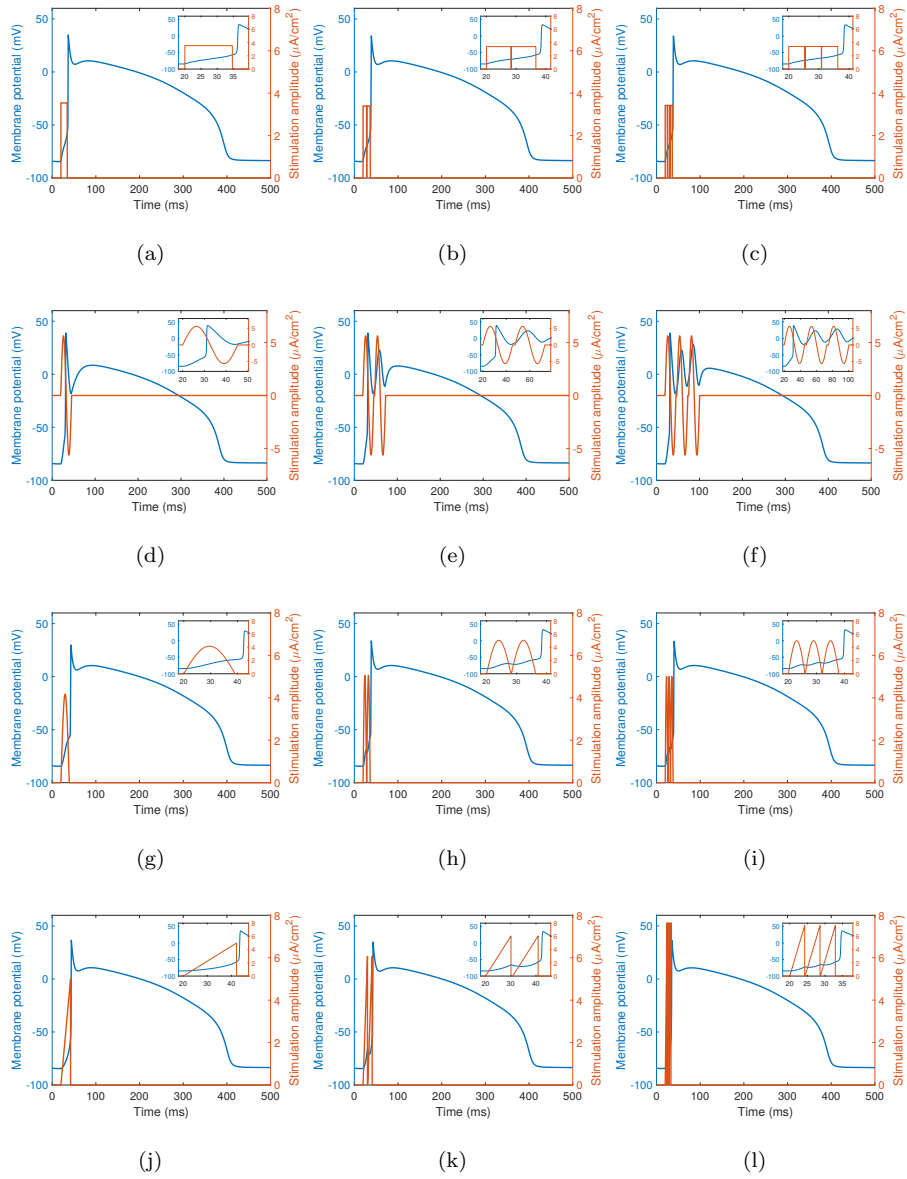


Figure 7: The optimized stimuli configurations from Table 3 applied to the *in-silico* cardiomyocyte: (a-c) rectangular pulse(s); (d-f) sine pulse(s); (g-i) half-sine pulse(s); (j-l) sawtooth pulse(s).

Table 3: The optimized configurations of the one pulse, two pulses and three pulses for different stimulation techniques that lead to the minimal energy consumption.

Pulse shape	Pulse(s)	$A$ [ $\mu\text{A}/\text{cm}^2$ ]	$t_d$ [ms]	$\tau$ [ms]	Energy [ $\text{pJ}/\text{cm}^2$ ]
Rectangular	1	3.54	14.71	-	<b>0.184</b>
	2	3.40	8.21	0.23	<b>0.189</b>
	3	3.42	5.36	0.10	<b>0.188</b>
Sine	1	5.63	25.33	-	<b>0.400</b>
	2	5.63	25.33	2.27	<b>0.801</b>
	3	5.60	25.30	2.30	<b>1.200</b>
Half sine	1	4.17	19.11	-	<b>0.166</b>
	2	5.06	8.14	0.11	<b>0.208</b>
	3	5.00	5.93	0.10	<b>0.222</b>
Sawtooth	1	4.99	22.11	-	<b>0.184</b>
	2	6.07	10.07	0.71	<b>0.247</b>
	3	7.65	4.25	0.10	<b>0.249</b>

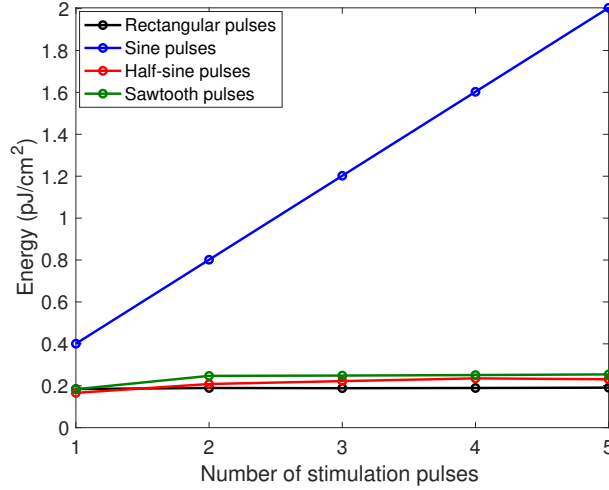


Figure 8: The optimized energy consumption depending on the number of stimulation sessions/pulses; the result is obtained by the surrogate algorithm.

266 shown in Fig. 9. In addition, the sine pulses expectantly cost the maximal  
 267 energy compared with other stimulation configurations. The sine wave is a bi-  
 268 phase stimulation with both positive and negative stimulation periods. As the  
 269 cell membrane is regarded as the capacitor in the underlying computational model,  
 270 the stimulation charges the capacitor during positive periods and discharges

271 during negative periods, which negatively reflects the energy required to induce  
 272 the excitation leading to action potentials.

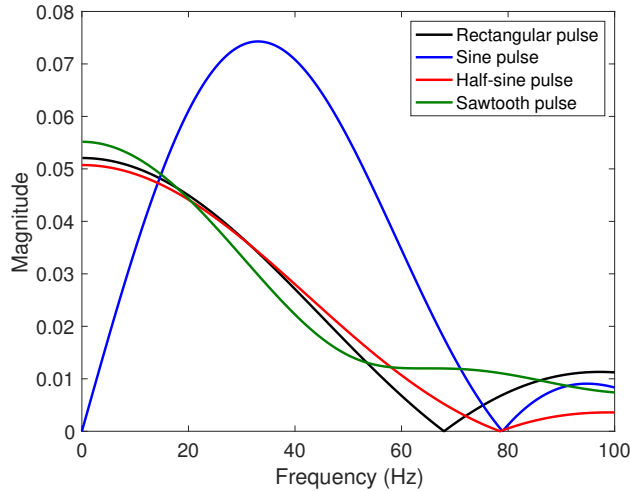


Figure 9: Magnitude of the Fourier transform of one-pulse stimulation signals with parameters given in Table 3.

### 273 3.2. Comparison between *In-silico* and *In-vitro* Data

274 A full experimental dataset is published in [37]. For appropriate comparison  
 275 between the corresponding theoretical dataset and a subset of the experimen-  
 276 tal dataset, both the simulation and experiment employed fixed pulse duration  
 277 pulses ( $t_d = 5$  ms) and, in the case of stimulus trains, fixed inter-pulse intervals  
 278 ( $\tau = 5$  ms). In the simulation, current amplitudes were varied in order to find  
 279 optimal values by using the surrogate optimization algorithm. In the experi-  
 280 ment, the threshold voltage, assumed to be linearly related to the current, was  
 281 determined by following calcium activation of the cardiomyocytes after applica-  
 282 tion of a stimulus train.

283 We compare normalized simulation and experimental data in terms of the  
 284 stimulation amplitudes in Fig. 10(a). The two data sets exhibit the same trend,  
 285 as reducing the amplitude of the stimulation and increasing the number of pulses  
 286 effectively depolarizes the cell membrane. However, we observe lower amplitude

287 values for the simulation data compared with the experimental data, indicating  
 288 imperfection of the employed LRd model (developed for a guinea pig ventricular  
 289 cell) to quantitatively predict outcomes in mouse cardiomyocytes. We also com-  
 290 pare energy consumption in the simulations and cell experiments in Fig. 10(b).  
 291 Again, the data sets exhibit similar trends, as reducing the amplitude of the  
 292 stimulation and increasing the number of pulses progressively increases energy  
 293 consumption.

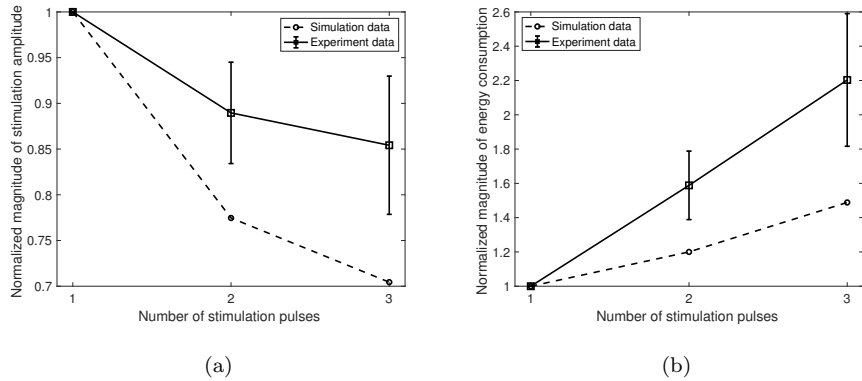


Figure 10: Comparison of the simulation- and experimental data: (a) in terms of the normalized actuation amplitudes; (b) in terms of the normalized stimulation energy. All amplitudes/energy are normalized to one-pulse stimulation values. The one-pulse duration is 5 ms, and the interval between consecutive pulses is 5 ms. All configurations induce action potentials in both *in-silico* and *in-vitro* cells.

294 Of note, it is not instructive to directly compare the results from Fig. 8 and  
 295 Fig. 10(b) since we optimized multiple parameters in Fig. 8 and only the stimu-  
 296 lation amplitude in Fig. 10(b), to ensure a fair comparison between simulation  
 297 and experimental data.

#### 298 4. Concluding Remarks

299 In this study, we determined that the minimal energy required to elicit a  
 300 cardiomyocyte action potential is approximately 0.166 pJ/cm<sup>2</sup> for a unit mem-  
 301 brane resistance. This value was obtained using a single-pulse half-sine cur-

302 rent injection with a peak amplitude of  $4.17 \mu\text{A}/\text{cm}^2$  and duration of 19.11  
303 ms provided by the nano-actuator. Note, however, that the load imposed by  
304 the neighboring cardiomyocytes could affect optimal pulse configuration and the  
305 computed energy levels when considering non-isolated cell stimulation as part of  
306 cardiac tissue. As a reference, the energy consumed for a 2 V stimulus with 0.3  
307 ms duration applied via 6 mm in diameter electrode, typically encountered in  
308 conventional pacemakers, is  $1/\pi \times 10^{10}$  pJ/cm<sup>2</sup> per unit resistance, ten orders  
309 of magnitude higher than the energy used to actuate a cardiomyocyte.

310 To be biologically relevant, the results presented in this study critically de-  
311 pend on:

- 312 • The performance of the LRd computational model, which was developed  
313 for a guinea pig ventricular cardiomyocyte. As presently demonstrated,  
314 the model does not fully reproduce the experimental quantitative outcome  
315 obtained from a mouse ventricular cardiomyocyte. These differences are  
316 particularly notable when sub-threshold stimuli are applied, since the re-  
317 sistance of the cellular membrane does not linearly change with stimulation  
318 time, implying alterations in sensitivity. The LRd model insufficiently ac-  
319 counts for these changes, limiting its ability to compare multiple-pulse and  
320 single-pulse stimuli.
- 321 • The resistance of the cell membrane, which is assumed constant, although  
322 the ionic channels dynamically open and close potentially changing the  
323 membrane resistance which would impact the obtained results.

324 Thereby, more precise computational models are required, in particular ones  
325 which properly address: 1) the sub-threshold cell dynamics, 2) the membrane  
326 resistance dynamics, and 3) the electrical load imposed by neighboring cardi-  
327 omyocytes. In terms of the experimental verification, *in-vitro* experiments that  
328 fully replicate *in-silico* experiments are required. In this work, although the  
329 direct current injection applied in the *in-silico* experiments and the applied  
330 electrical field applied in the *in-vitro* experiments both demonstrated a similar  
331 trend regarding energy consumption, their energy-efficiencies are different. The

332 direct current injection strategy is more energy-efficient than the applied electric  
333 field strategy which dissipates a large portion of energy in the bath solution.  
334 Ultimately, the energy expenditure of the overall nano-actuator will be addi-  
335 tionally depending on the energy used for sensing and communications; values  
336 which are yet to be determined.

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