ANALOG AND MIXED-SIGNAL CIRCUIT DESIGN AND TECHNIQUES FOR BIOELECTRICAL SIGNALS

M.S. Oral Defense

by

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GWC 208C

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Motivation

- Why cells study?
- How to research cells?
- Why VLSI circuits for cell research?
- What are the electrical properties of cells?

Overview

Part One: A switched-capacitor based capacitance sensor design chip including a temperature readout circuit, a Bandgap reference circuit and various testing structures is presented. Circuit analysis, simulation verification, implementation and testing plans are presented.

Part Two: A 3 stage amplification circuit for HL-1 cardiac cells action potential measurement has been implemented and tested; A phase detector for cardiac array measurement circuit has been designed and simulation verified; a 2nd order sigma-delta analog-to-digital-converter and a 1st order sigma-delta digital-to-analog-converter have been simulation verified.

Part One
Capacitance sensor chip

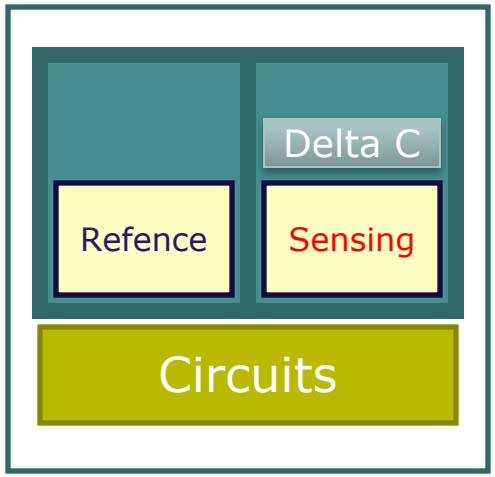
Why we need a capacitance sensor for study of cells

1. Capacitance Change occurs with charges moving

Capacitance change occurs when chemical or voltage change causes charges to move in and out of the cell membranes through ion channels.

2. Most bio-molecules have high affinity to attach to a surface coated by specific receptor molecules. If the type of molecule coated on a surface as a receptor is known and there is binding observed, then the molecules that bound to the surface can be determined. This results in a surface capacitance change that can be measured.

Capacitance Sensor Principles



Delta C
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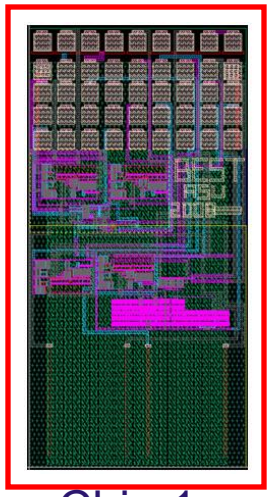
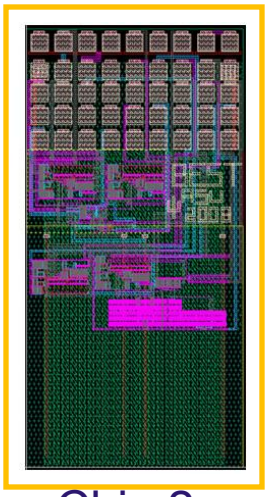
Voltage Output

\+ Other Circuits



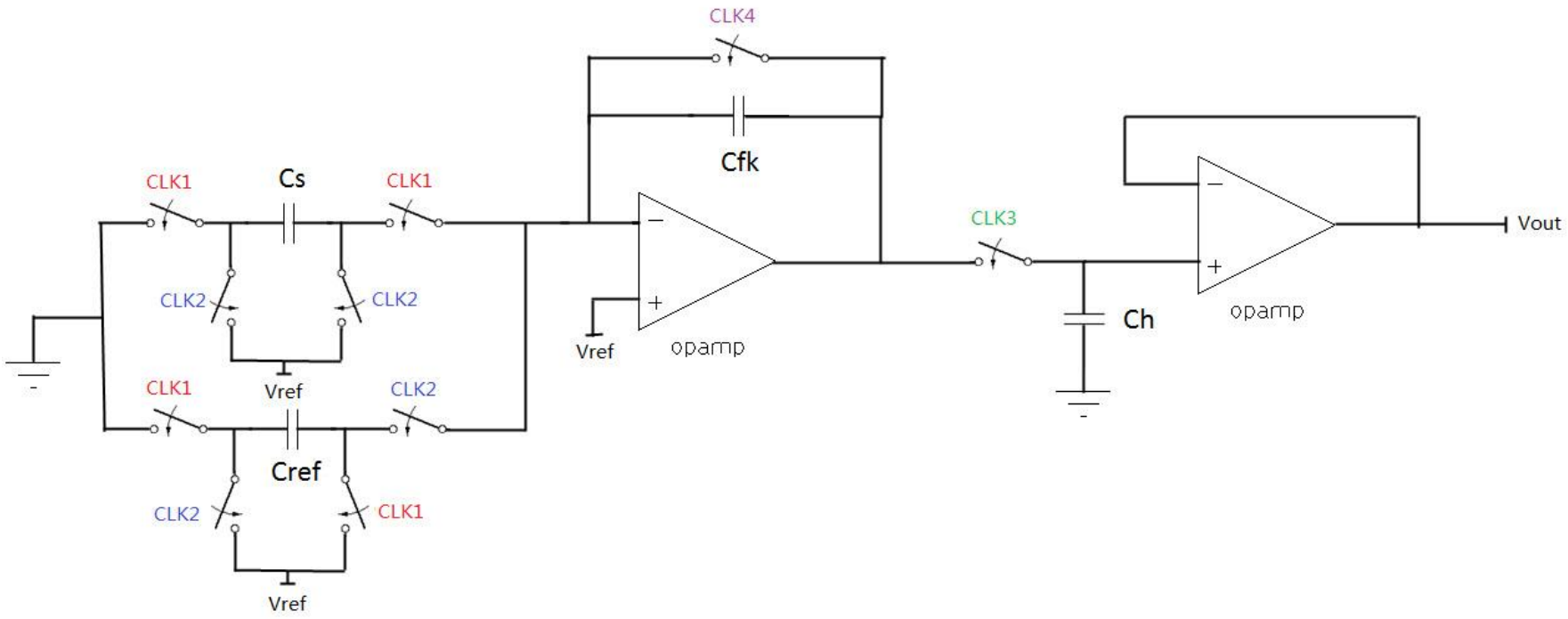
Chip 1



Chip 2

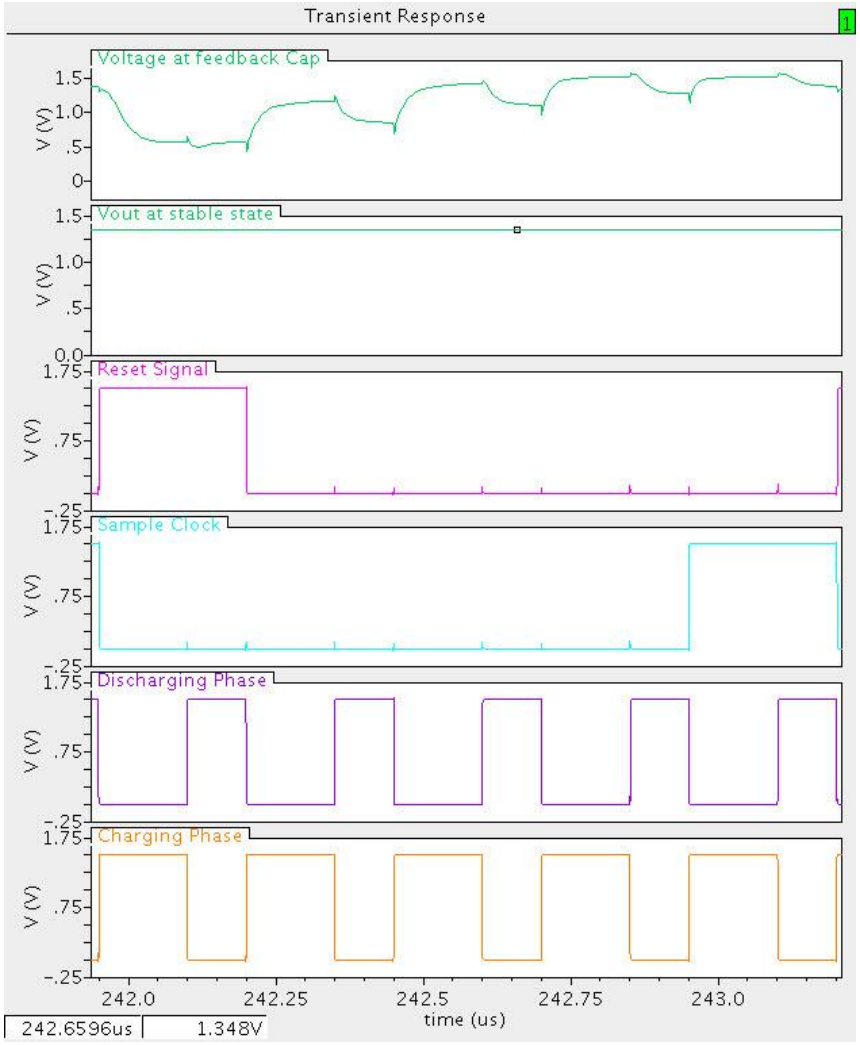
The time of integration is controlled by external clock input signals.

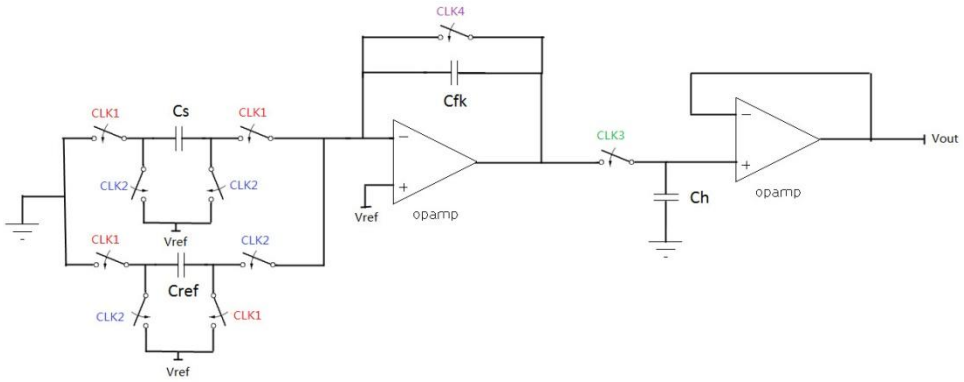
Capacitance Sensor Diagram



Design was fully simulation verified. The simulation environment tool used was Cadence IC 6 analog environment simulator; simulation models are from MIT/Lincoln Labs 3D SOI 0.15 um technology. Cadence Spectre model version is 3DIC 3.3.5.

Capacitance Sensor Simulation Result





Transient Response over a shorter period, 3 complete charging and discharging cycles, with voltage at Cfk, voltage at Cout and four clock signals (CLK4: Reset Signal, CLK3: Sample Clock, CLK2: discharging Cfk phase, CLK1: charging Cfk phase), respectively from top to bottom.

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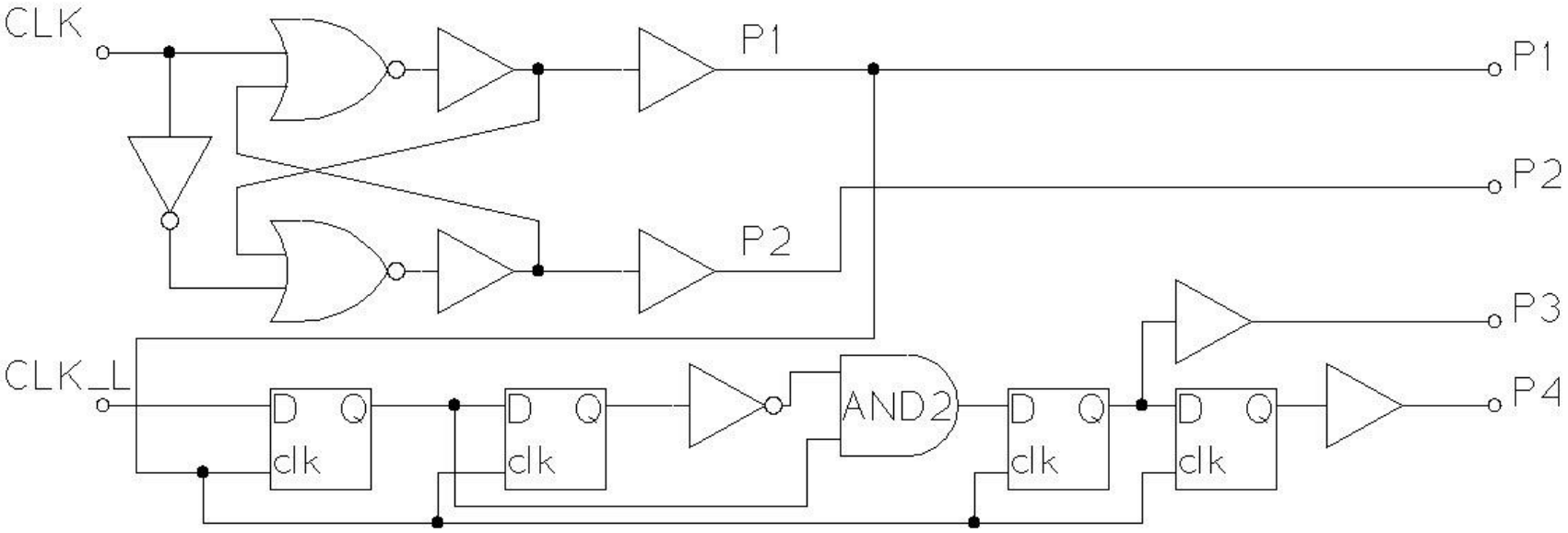
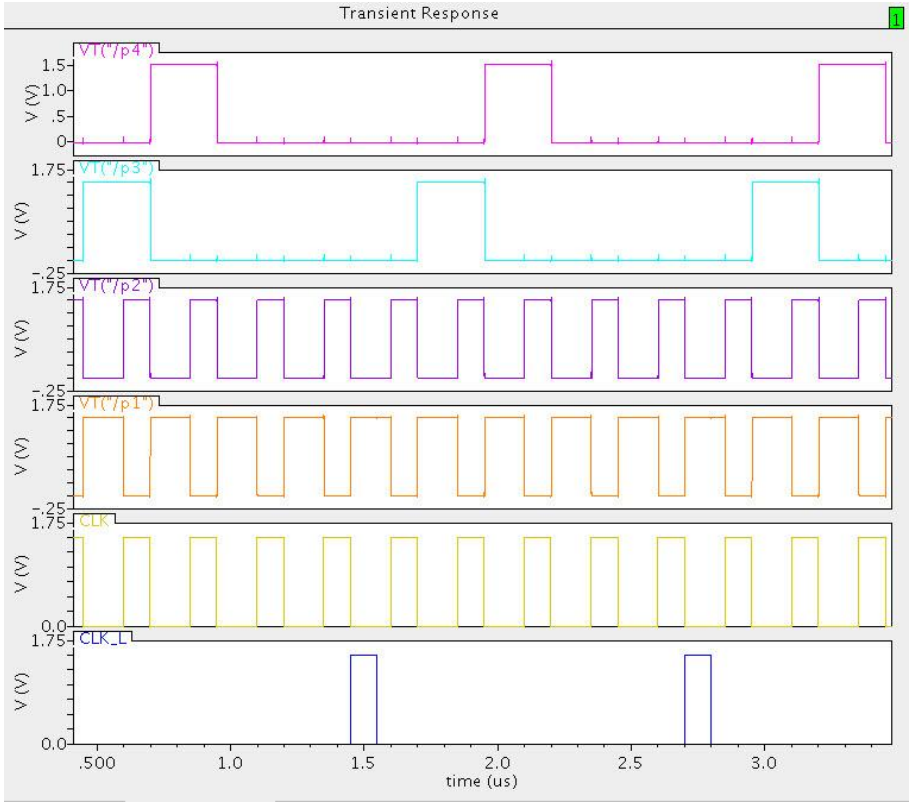
Four-phase clock generation circuit



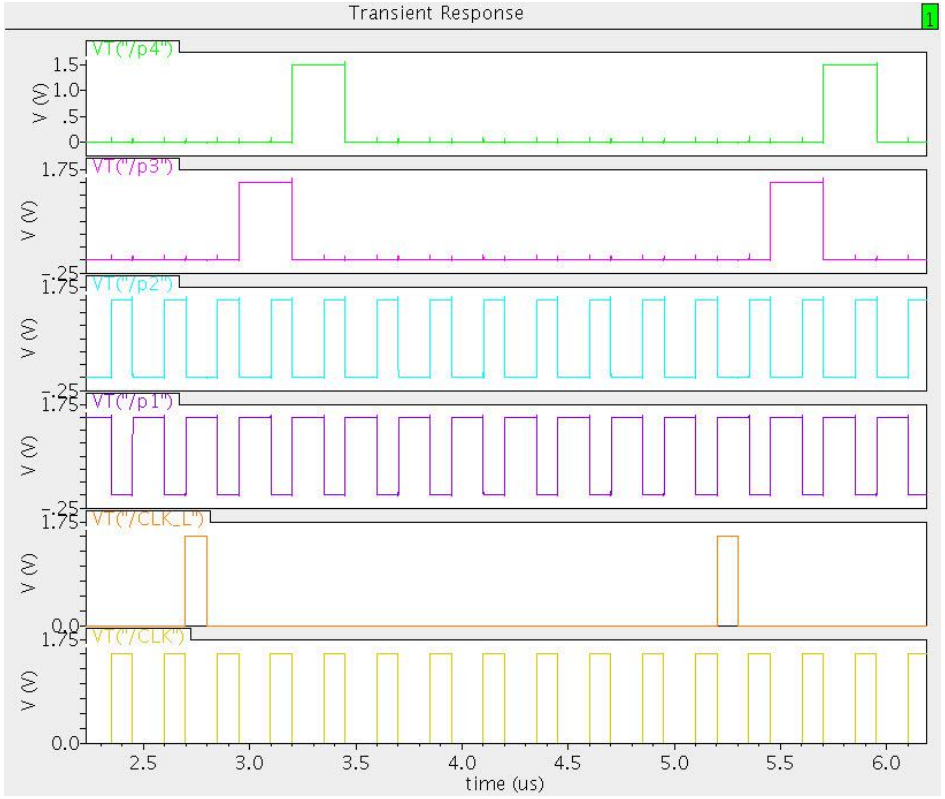
Four-phase clock generation circuit

The principle the capacitance sensors are based on is charging and discharging the capacitors, which are the sensing and reference capacitors. Inside the switched-cap circuit, the clock signals controlled the charge integrations on the feedback capacitors.

Four-phase clock generation circuit simulation

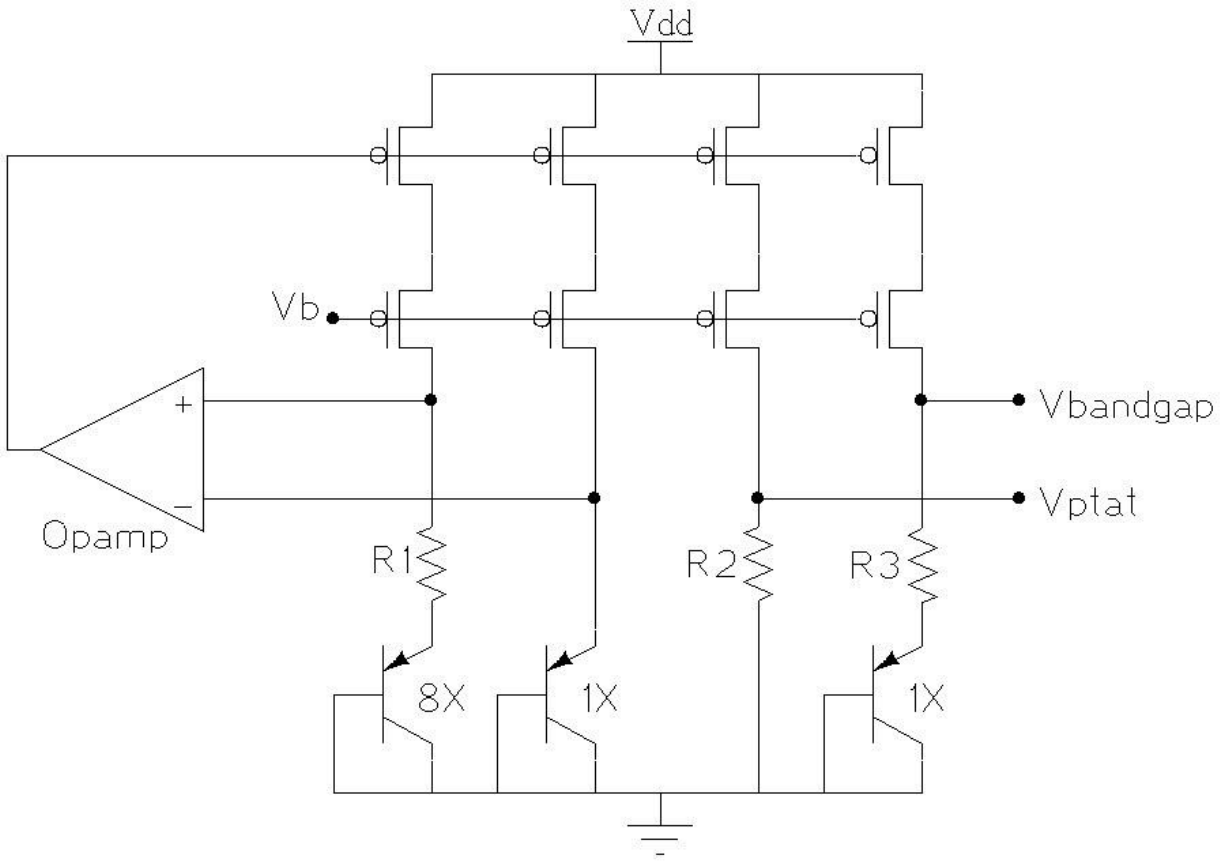


Four-phase clocks generation waveform 1



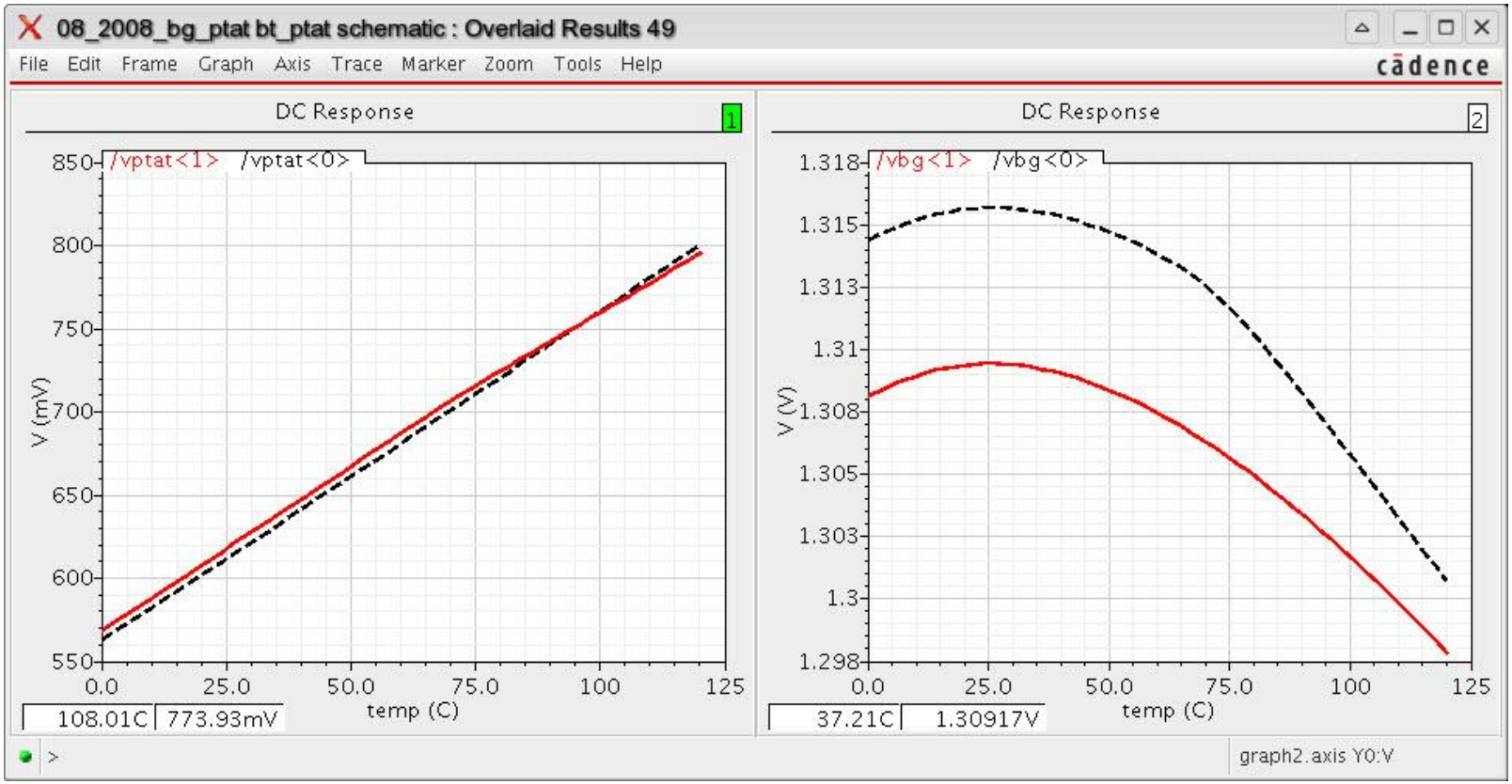
Four-phase clocks generation waveform 2

Bandgap & PTAT Temperature circuit



Proportional-to-absolute-temperature Circuit and Bandgap circuit diagrams

Bandgap & PTAT Simulation



Simulation results of Bandgap reference and PTAT under resistance variations of +20% (dashed black line) and -20% (solid red line)

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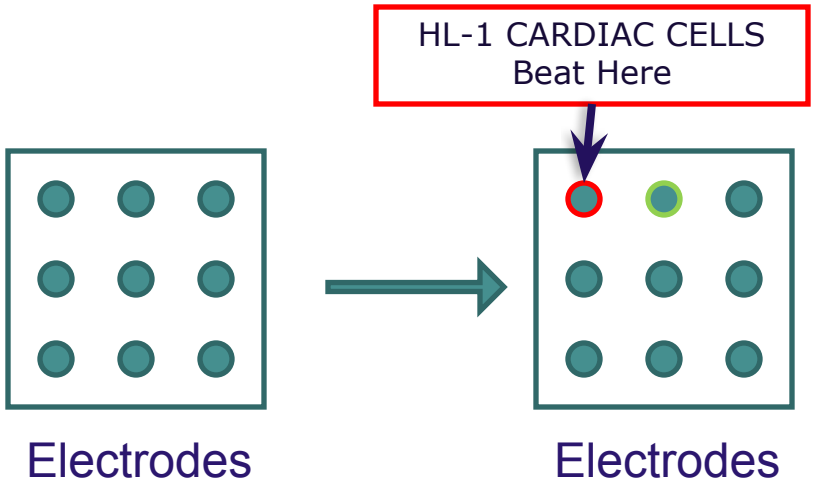
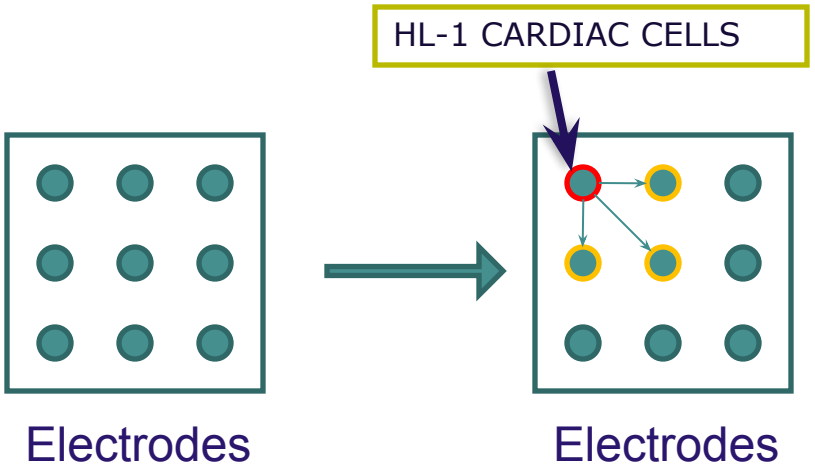
Part Two

HL-1 Cardiac Cells Study

Two ways to study HL-1 Cardiac Cells

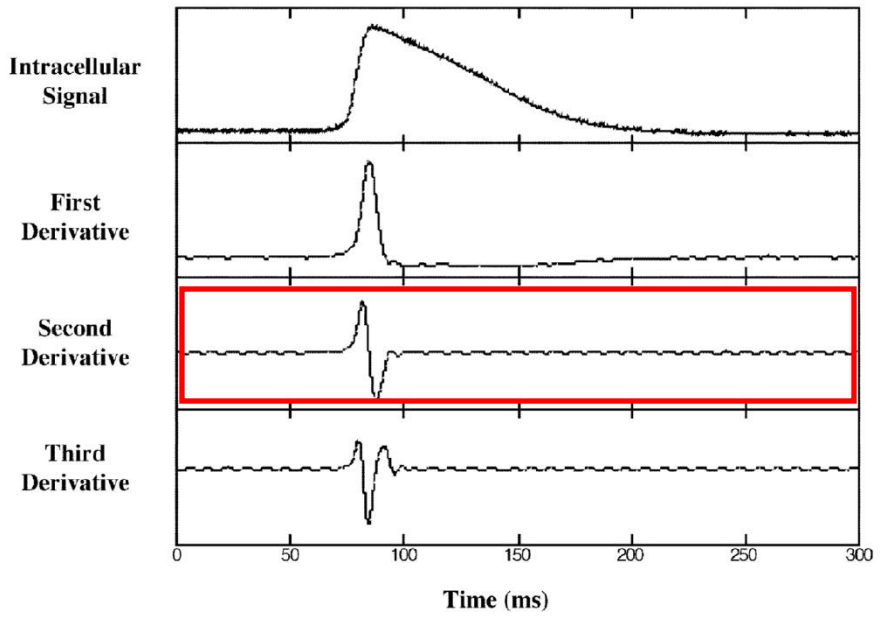


The first way is focusing on the waveform that we observe on a single electrode.



The second way is to determine the delay in time domain from two different electrodes.

AMPLIFICATION CIRCUIT FOR HL-1 CARDIAC CELLS ACTION POTENTIAL MEASUREMENT

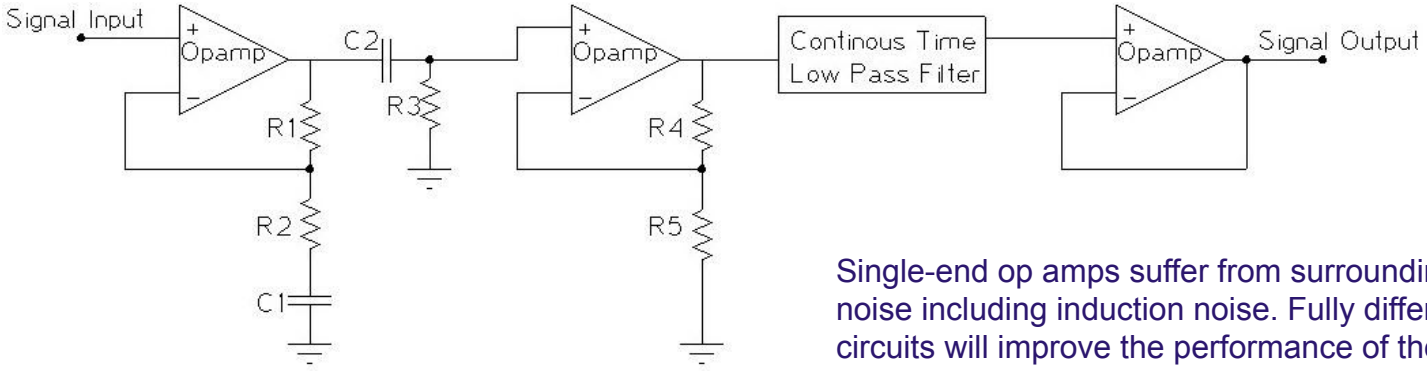


A typical HL-1 intracellular signal recorded with whole-cell patch clamp and the derivatives are shown. Extracellular recordings resemble the second derivative [2]

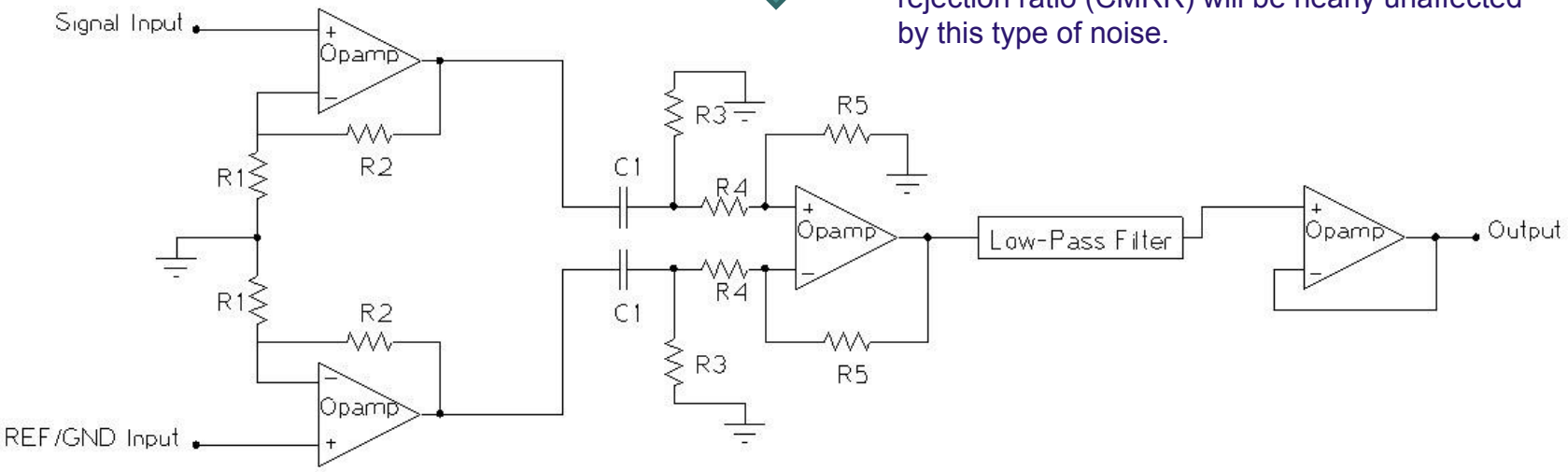
Action potentials in cardiac cells are intracellular signal across the cell membrane. When microelectrode recording methods are used, only the second derivative of the signal can be detected due to the low seal resistance between the cell and the electrode]

[1] D. A. Borkholder, “Cell-based biosensors using microelectrodes,” Ph.D. dissertation, Stanford University, 1998.
[2] G. T. A. Kovacs, “Electronic sensors with living cellular components,” *Proceedings of the IEEE, vol. 91, pp. 915–929, 2003*

AMPLIFICATION CIRCUIT FOR HL-1 CARDIAC CELLS ACTION POTENTIAL MEASUREMENT



Single-end op amps suffer from surrounding noise including induction noise. Fully differential circuits will improve the performance of the system by canceling out noise from connection wires and other parasitic in the system. Since the noise is mostly common to both input nodes, amplifiers with good common-mode rejection ratio (CMRR) will be nearly unaffected by this type of noise.



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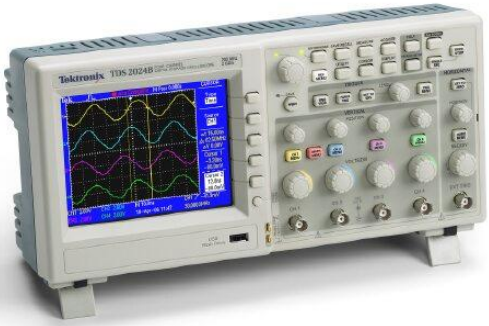
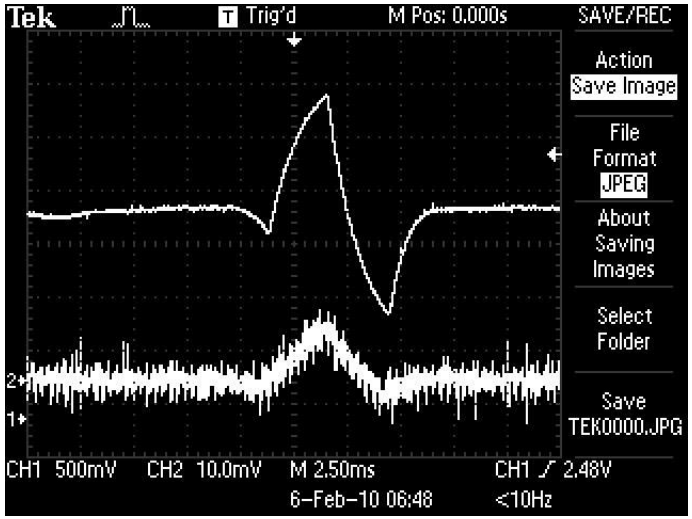
AMPLIFICATION CIRCUIT FOR HL-1 CARDIAC CELLS ACTION POTENTIAL MEASUREMENT

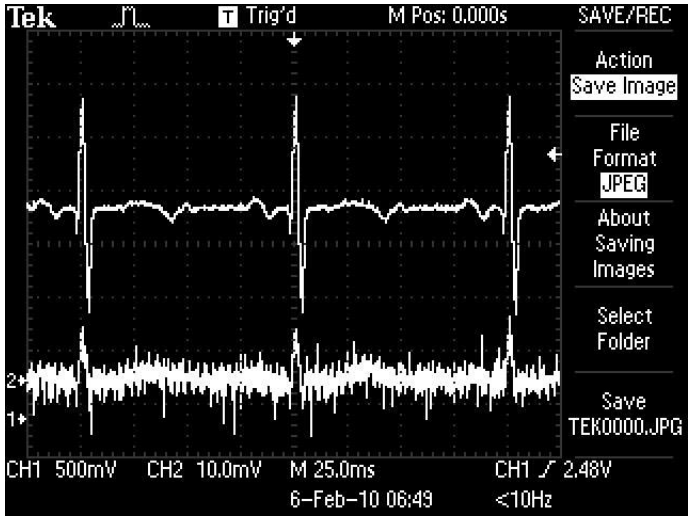


TDS1000 Series oscilloscope

Keithley Arbitrary Waveform Generator Model 3390

Input signal similar to the expected cardiac signals but with an amplitude of 6.3 mV pk-pk





J. Song, D. Welch and J. Christen, "Amplification Circuit and Microelectrode Array for HL-1 Cardiomyocyte Action Potential Measurement", 2010 IEEE International Symposium on Circuits and Systems

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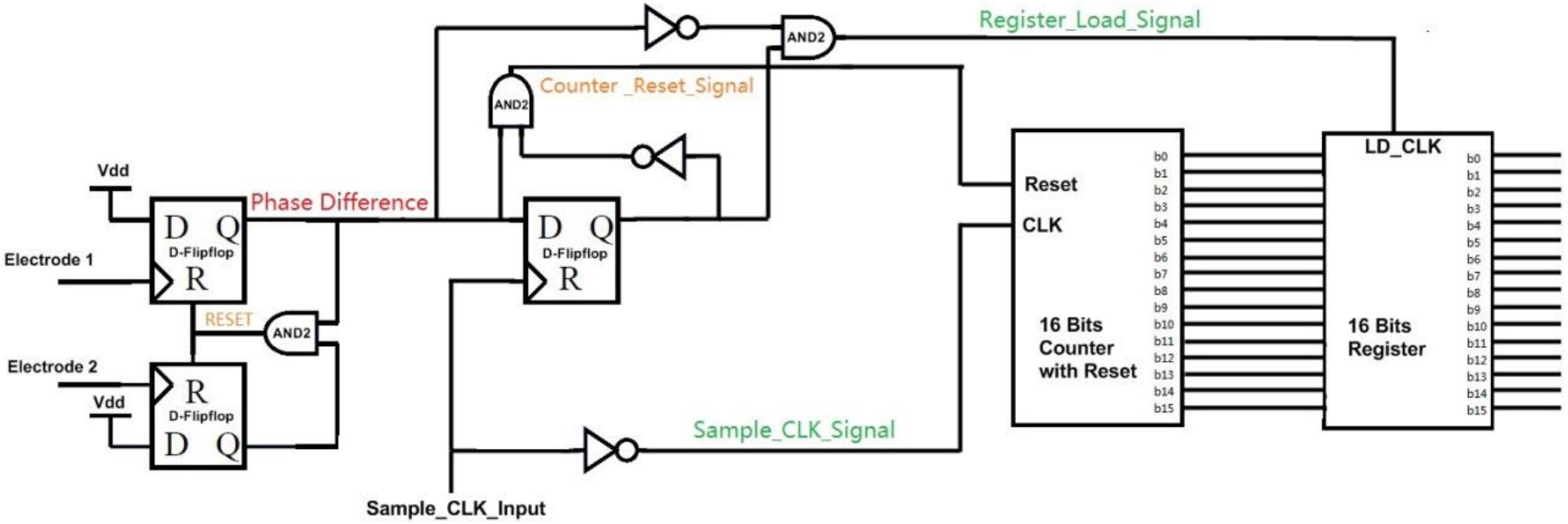
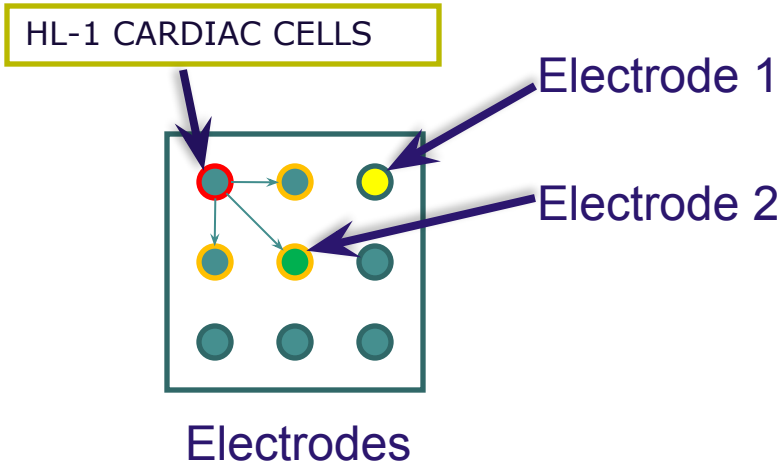
Phase Detector Circuit





Phase detectors are used to detect the delay of between two signals in the time domain. A phase detector circuit is to measure the propagation delay between action potentials in a array of electrodes over which cardiac cells have been cultured.

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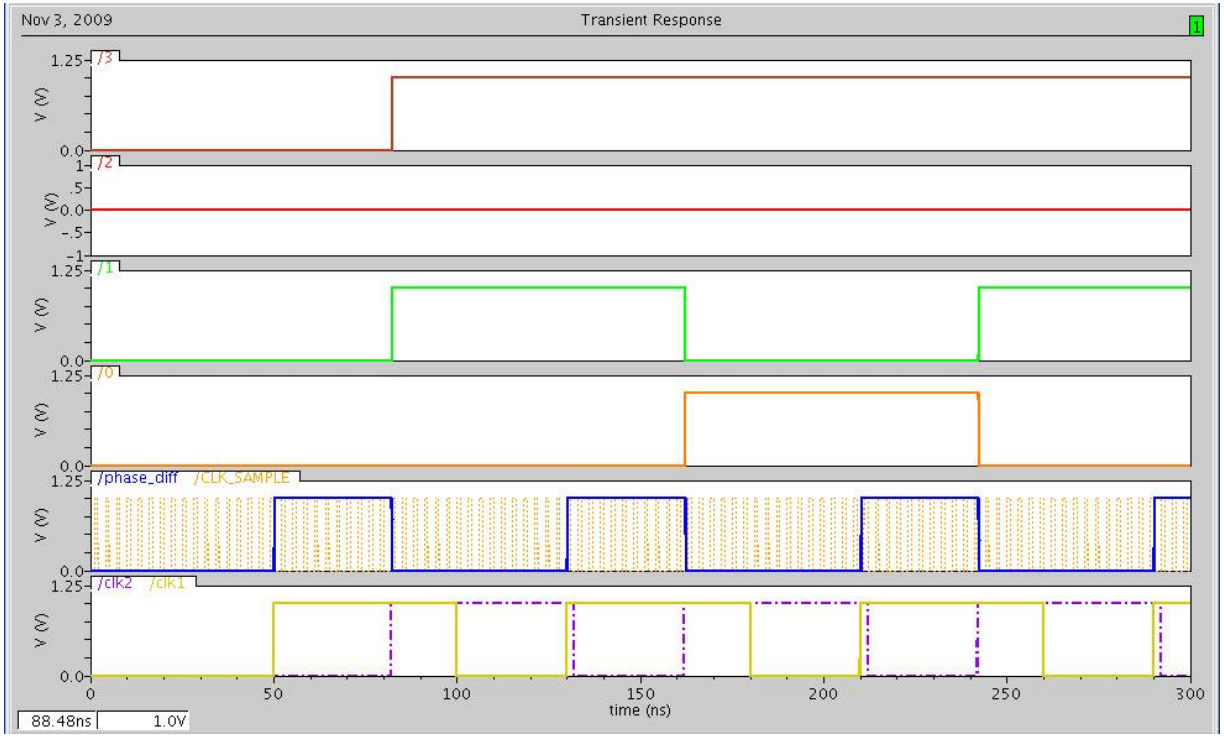
Phase Detector Circuit Simulation



The first phase difference pulse has 10 rising edges of the sampling clock signal within this single pulse, the digital outputs from bit 0 to bit 3 are “0101” which is 10 in decimal. The second phase difference pulse has 9 rising edge of sampling clock signals within this pulse period, and the digital outputs from bit 0 to bit 3 are “1001” which is 9 in decimal. The third phase difference pulse also has an output of 10 in decimal.

Summary

Two chips were taped out in December 2008. They included two designs of capacitance sensors, a PTAT temperature sensing circuit and a bandgap reference. The fabrication technology is provided by MIT Lincoln Lab. Each chip is fabricated by stacking and bonding three wafers. Each wafer is fabricated in the IBM 0.15mm SOI technology.

Two different version of board level discrete components amplification circuits for HL-1 cardiac cells have been designed and tested. A phase detector circuit which will be used to measure the propagation delay between two electrodes has been designed and simulation verified.

A 2^{nd} Sigma Delta analog-to-digital and a 1^{st} order digital-to-analog converter has been simulation verified.

Thank you!