John R. Zaleski, Ph.D., CPHIMS
john@medicinfotech.com

A Chemoreceptor-Based Sinoatrial Heart Controller Device Concept (originally written August 2002)

Abstract

This invention is targeted at providing a mechanism for automatically controlling the pacing (heart rate) and contractile force (stroke volume) of either an artificial left ventricular assist device (LVAD) or a patient's own heart who has experienced degenerative performance of the Sinoatrial node. The device operates by analyzing the chemical nature of the epinephrine, norepinephrine, and dopamine content of the return blood flow through the superior vena cava and then using this information via cyclic voltammetry, neural network control, and feedback to the pacing device to control the heart rate of the assist device.

Background Information

The concept is for a device that measures the chemical content of the blood flow past the sinoatrial node, processes the chemical content via cyclic voltammetry to determine the amount of epinephrine (EPI) and norepinephrine (NE), and uses this information to establish the resting and various pacing heart rates of a left ventricular assist device.

Artificial assist devices that exist today normally operate by controlling heart rate based on Proprioceptors–position of limbs & muscles during physical activity, or Baroreceptors–monitor blood pressure in major arteries & veins. None to date operate on the basis of Chemoreceptors: monitoring changes in chemical makeup of the blood stream in direct response to epinephrine production by the adrenal medulla. Such changes are, however, more consistent with the operation of the human heart. For instance, heart rate varies not only according to mechanical movement of limbs, but also as the result of changes in emotion. Such changes manifest themselves as changes (increases and decreases) in sympathetic and parasympathetic hormones. Sympathetic hormones (epinephrine, norepinephrine) tend to increase stroke work and heart rate, whereas parasympathetic hormone (acetylcholine) tend to lower hear rate. These two hormones operate to control the resting rate of the heart and its changes as a result of higher-brain center changes (including production of hormone by the adrenal medulla). Benefits of achieving this capability include a more naturally-behaving artificial hearts, or, in the case in which a human heart is merely being paced by an assist device, to control normal heart function in relation to changes in hormone production. Thus, the controller described herein provides an adjunct to existing controllers.

Autonomic regulation of heart rate is controlled via one of the following specific systems within the body:[1]

1) Proprioceptors – position of limbs & muscles during physical activity
2) Chemoreceptors – monitor chemical changes in blood
3) Baroreceptors – monitor blood pressure in major arteries & veins
4) Higher brain centers

Current artificial heart assist devices operate using feedback from items (1) and (3) alone. Long-term (weeks to months) artificial heart assist devices popularly used for ventricular support, all under auspices of NHLBI, are as follows:[2]

1) Abiomed extracorporeal, pneumatically-driven, pulsatile, left, right, or biventricular, introduced in 1988, FDA approved for in-hospital use for low output syndrome.
2) Thoratec extracorporeal, pneumatically-driven, pulsatile, left, right, or biventricular approved for in-hospital use for post cardiotomy low output and as a bridge to transplantation.
3) TCI (Heartmate) implantable, pulsatile pneumatically-driven, approved for in-hospital use as a bridge to transplantation. The electrically powered totally implanted configuration with a wearable power source, trans-cutaneous power lead and vent, is approved for in-hospital as well as out-of-hospital use for bridging to transplantation and is currently used under IDE in the randomized REMATCH trial.
4) Novacor implantable electric, pulsatile, left ventricular, wearable power source, transcutaneous power lead and vent, is approved for in-hospital and out-of-hospital use for bridge to transplantation.

The NHLBI has recommended that "…a large population exists that could benefit from mechanical replacement of the heart. Recent increased application of ventricular assist suggests that this modality will be adequate for a portion of over 100,000 annual candidates but will not be applicable to 5-10% that would be well served by a TAH. There are no emerging therapies that can fill this need. The clinical experience with the use of VADS [ventricular assist devices] along with the progress made in TAH

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[1] source: http://www.southalabama.edu/biology/shardo/bly152/cardiovascular/heart_electric_nonav.html (Accessed 8/23/02)

[2] Source: NHLBI: "Expert Panel Review of the NHLBI Total Artificial Heart (TAH) Program: June 1998 – November 1999).

development supports the proposition that a clinically effective TAH is an achievable objective."[3]

Furthermore, publications[4] focusing on advances in heart assist devices have identified characteristics desired for upcoming artificial organs. These include (1) miniaturization, (2) interfaces with nerves for automatic control, (3) control systems that are acceptable for both the living body and the embedded artificial organs, and (4) harmonization with the living body in various ways, including interfaces with higher brain centers and reduction of thrombus (and the associated foreign body rejection issues).

In addition, "the neuronal and hormonal control of the circulation, including the control of the heart, is mainly effectuated by the autonomic nervous system and its hormonal transmitters, the catecholamines… Autonomic control of the circulation primarily operates through the sympathetic system, though to a slight extent through parasympathetic signals to the heart. These have been lumped together, and there are basically three separate feedback mechanisms in this computational block. These are (1) feedback from the baroreceptor control system; (2) feedback from the peripheral chemoreceptors in the carotid and aortic bodies, and (3) feedback control of the circulator system caused by central nervous system ischemia, that is, ischemia of the vasomotor center in the brainstem. Another input that affects the autonomic nervous system is also included: The activation of the autonomic nervous system during exercise."[5]

Methods for measuring serum epinephrine levels exist. WPI[6] offers an "ultra-sensitive and low noise carbon fiber (CF) and carbon disk (CD) electrodes can be applied with their Micro-C Potentiostat in the electrochemical detection of catecholamines (epinephrine, norepinephrine, and dopamine)." The CF30-500 model shows current output in PicoAmperes versus Dopamine concentration (ng/ml). Sample data points: 10 ng/ml → 10 pA; 1000 ng/ml → 1000 pA; 100000 ng/ml → 100000 pA. CF electrodes have diameters ranging from 10 to 30 microns with excellent linearity and can detect compounds as low as 0.2 nM. "Because of their ultra-low noise performance (<5 micro Volts) the CD electrodes are …suitable for in vivo or in vitro extracellular recording especially where action potentials are recorded from small interneurons which may be difficult to isolate with other methods.

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[3] Ibid.

[4] Source: 6th International Micromachine Symposium Special Lecture: "Artificial Heart Research by the Use of Micromachines." Lecture by Sinichi Nitta, Vice President of Tohoku University and Professor of the Institute of Development for Aging and Cancer

[5] International Journal of Bioelectromagnetism, Number 2, Volume 2, 2000, page 8. "Neuronal and hormonal cardiac control processes in a model of the human circulatory system," E. Naujokat, U. Kiencke—Institute of Industrial Information Technology, University of Karlsruhe, Germany

[6] World Precision Instruments: "Carbon Fiber and Carbon Disk Microelectrodes."

"Extracellular recordings using CD electrodes (CD-30) in CA1 region of the hippocampus in an anesthetized rat shows ultra-low noise (<5 micro Volts)." Response in same region varied between +50 and –100 micro Volts with response time less than 5 milliseconds. A sample bio-sensing device is illustrated in Figure 1.

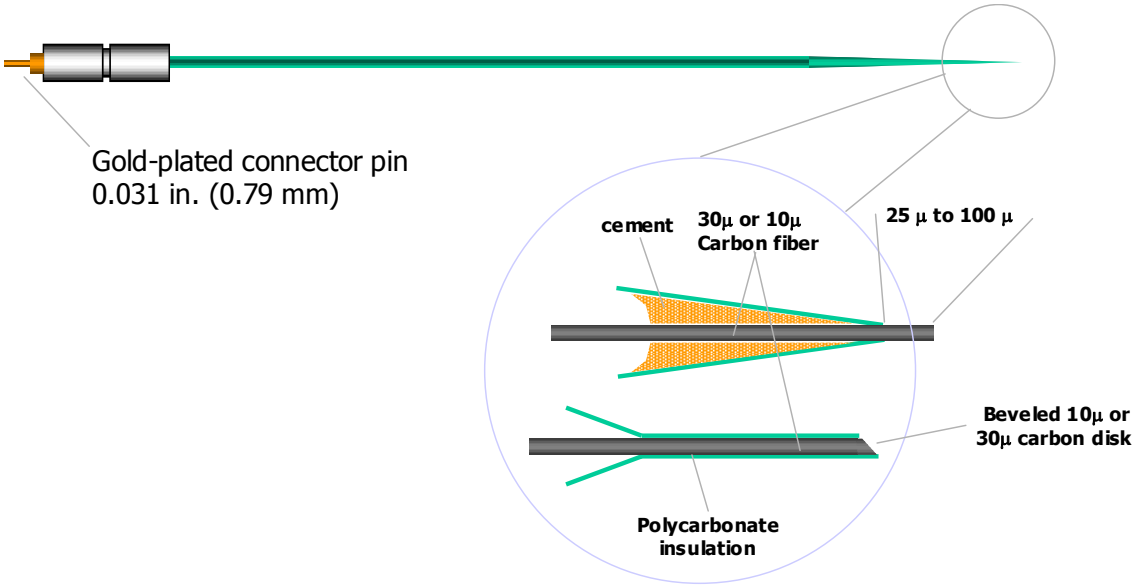

Figure 1: WPI bio-sensing device to measure current response to catecholamines using cyclic voltammetry. (Drawing recreated by author)

The following figure illustrates the manner in which electrical signals are conducted throughout the human heart.

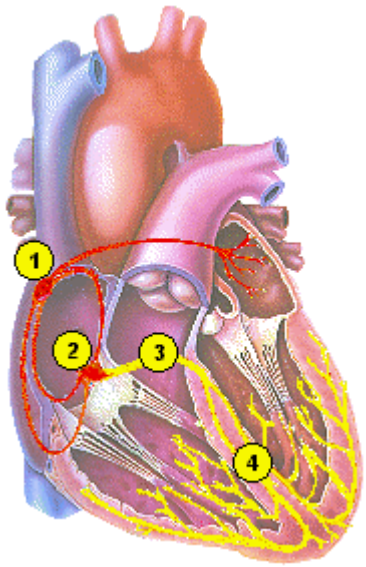

Figure 2: Sinaoatrial node (1) is located in rear wall of right atrium near opening of superior vena cava. It has the fastest rhythm (80-100 action potentials per minute) & overrides all others. Action potential travels through walls of atria causing atrial contraction. Internodal pathways (red lines) connect S-A node to A-V node (2). Atrioventricular node is the large node in right posterior portion of interatrial septum. It has a slower rhythm than S-A node (40-60 action potentials per minute). The A-V Bundle of His (3) is the only electrical connection between atria & ventricles. It divides into right & left bundle branches in ventricular septum. The Purkinje fibers (4) are distributed throughout the ventricular myocardium. These synchronize ventricular contraction. Source: http://www.southalabama.edu/biology/shardo/bly152/cardiovascular/heart_electric_nonav.html (Accessed 8/23/02).

Epinephrine is manufactured from Tyrosine according to the following process.[7]

[7] Source: ESA Clinical Method: "Determination of Urinary Metanephrine and Normetanephrine Without Extraction."

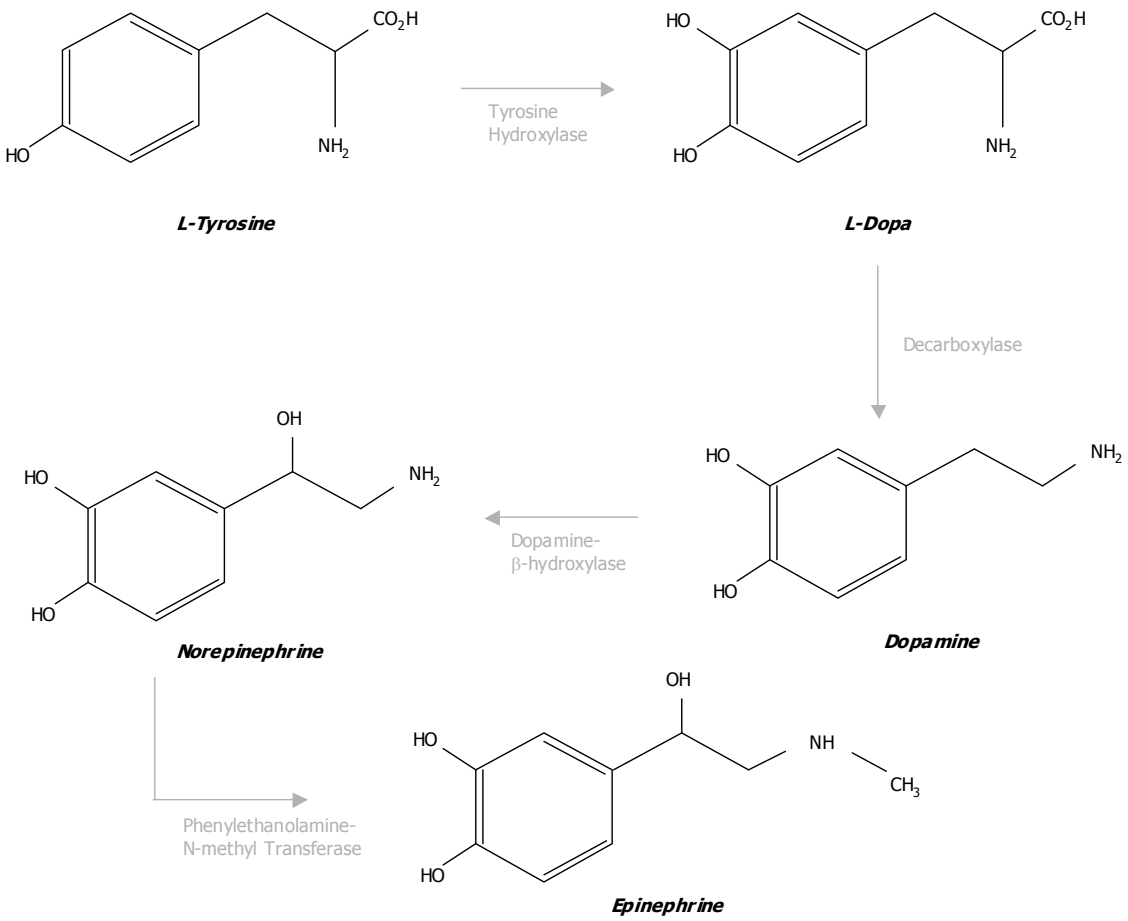

Figure 3: Epinephrine metabolism from amino acid Tyrosine. (Drawing recreated by author)

Epinephrine affects signal rapidity and strength in the sinoatrial node of the heart. Figure 4 illustrates aspects of signal firing, showing the chemical intracellular relationships and when they occur in time.

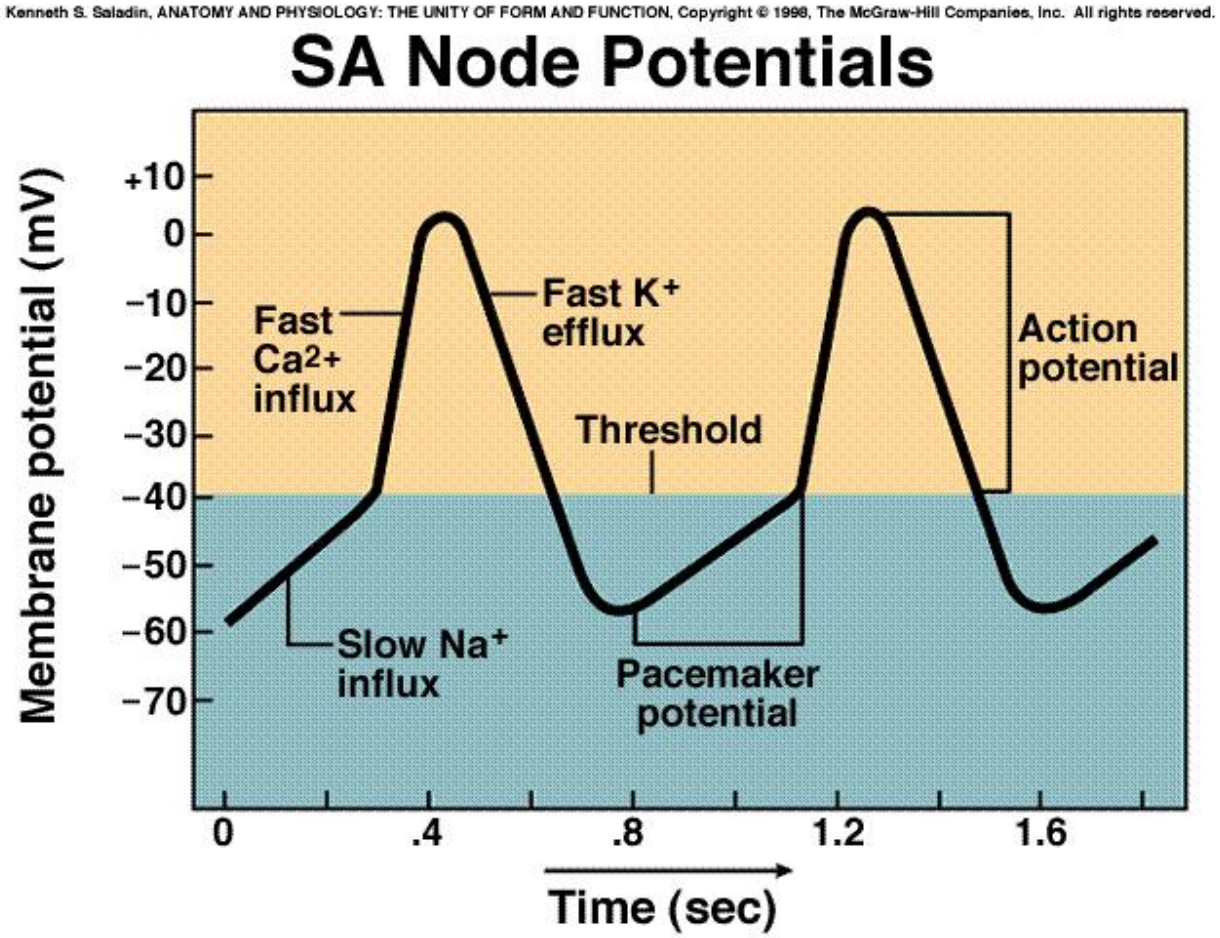

Figure 4 Sinoatrial node action potentials. Intracellular events driving repeated contraction and pacing of the heart: (1) Rapid depolarization—at threshold voltage-gated fast Na+ channels open, Na+ flows in, ~4 msec; (2) Extended plateau—Na+ channels close, voltage-gated slow Ca+2 channels open in SR & cell membrane, Ca+2 increases in cell cytoplasm, Ca+2 start to close after ~175 msec, produces longer contraction period; (3) Rapid depolarization—voltage-gated slow K+ channels open, K+ flows out, K+ channels close, Ca+2 is actively transported out of cytoplasm, ~75 msec; (4) Absolute refractory period (200 msec) lasts through most of contraction period (250 msec). Relative refractory period (50 msec), stimulus produces premature & smaller contractions. Source: http://www.southalabama.edu/biology/shardo/bly152/cardiovascular/heart_electric_nanav.html (Accessed 8/23/02)

Cells in adrenal medulla synthesize & secrete epinephrine and norepinephrine. Ratio of these catecholamines: human—80%; cat—60%; chicken—30%.[8] Synthesis of

[8] Source: Colorado State University--http://arbl.cvmbs.colostate.edu/hbooks/pathphys/endocrine/adrenal/medhormones.html (Accessed 8/23/02)

catecholamines begins with amino acid Tyrosine, taken up by chromaffin cells in the medulla and converted into norepinephrine and epinephrine. Secretion of hormones stimulated by acetylcholine release from preganglionic sympathetic fibers innervating the medulla. Many types of stresses stimulate secretion, including exercise, hypoglycemia, and trauma. Following secretion into blood, catecholamines bind loosely to and are carried in circulation by albumin and, perhaps, serum proteins.

"EPI & NE bind to adrenergic (that is, adrenalin receptive) receptors on surface of target cells:

Receptor	Binds	Effect
$\alpha 1$	EPI, NE	free Calcium $\Uparrow$
$\alpha 2$	EPI, NE	cyclic AMP $\Downarrow$
$\beta 1$	EPI, NE	cyclic AMP $\Uparrow$
$\beta 2$	EPI	cyclic AMP $\Uparrow$

Some major resulting effects:

1) Increased rate, force of heart muscle contraction (primarily EPI acting through beta receptors)
2) Constriction of blood vessels (NE)
3) Dilation of bronchioles
4) Stimulation of lipolysis in fat cells (provides fatty acids for energy production in tissues and aids in conserving blood glucose reserves)
5) Increased metabolic rate (O2 consumption and heat production increase in response to NE)
6) Dilation of pupils
7) Inhibition of certain 'non-essential' processes (for example, gastrointestinal secretion)

Adrenal glands (adrenal medulla) are found in pairs above each kidney. The average amount of epinephrine production is shown in the table below:[9]

[9] Source: www.cytochemistry.net/Endocrine0System/Adrenal_Lecture_slides_files (Accessed 8/23/02)

	Resting	Moderate Exercise	Heavy Exercise
EPI (pg/ml)	40	100	400

Epinephrine affects sinoatrial cells in the following way, as further illustrated with the aid of figure 5.[10]

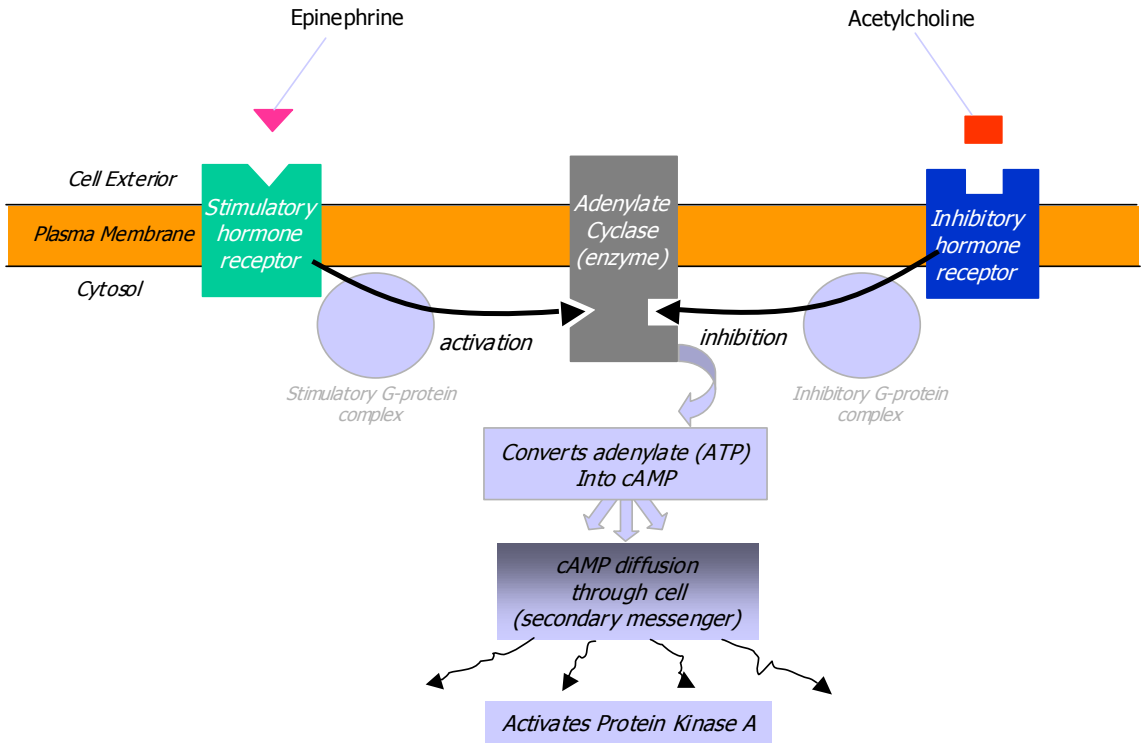

Figure 5: Metabolism method of Epinephrine and Acetylcholine at cellular level. (Drawing recreated by author).

"Enzyme 3,5-cyclic nucleotide phosphodiesterase (CAMP-PDE) converts cyclic Adenosine Monophosphate (cAMP) to non-cyclic Adenosine Monophosphate (AMP). Hormones affect a cell's activity by binding to specific hormone receptors that activate G-proteins. One such hormone is epinephrine. When EPI binds the beta-adrenergic receptor (adrenergic means adrenalin activated), this activates a G-protein that in turn activates an enzyme called adenylate cyclase that converts ATP (adenylate) into cAMP. The cAMP produced by adenylate cyclase then diffuses through the cell and acts as a 'secondary messenger': activating various enzymes including Protein Kinase A (PKA). PKA is important in the heart, where increased PKA activity increases the responsiveness of heart muscle cells (cardiomyocytes) to the Calcium

[10] Source: MadSci Network: "How and why does caffeine affect the pulse rate of a person?" Michael Onken, Washington University, Accessed February 2000.

currents that control beating. PKA does this by adding phosphate molecules ('phosphorylating') …that regulate heart functions, like membrane channels and contractile proteins."[11]

The net reaction of this binding is this: epinephrine results in increased cAMP levels, affecting several cellular processes by activating PKA.

Heart rate is thereby determined by the cells in the sinoatrial node. Cells depolarize and initiate contraction of the atria. Ventricles are then stimulated to contract via activation of AV node and subsequently the purkinje cells. Heart rate is set by rate of depolarization of the sinoatrial node. A graphic illustrating the sinoatrial action potential in relation to ventricular is shown in figure 6.

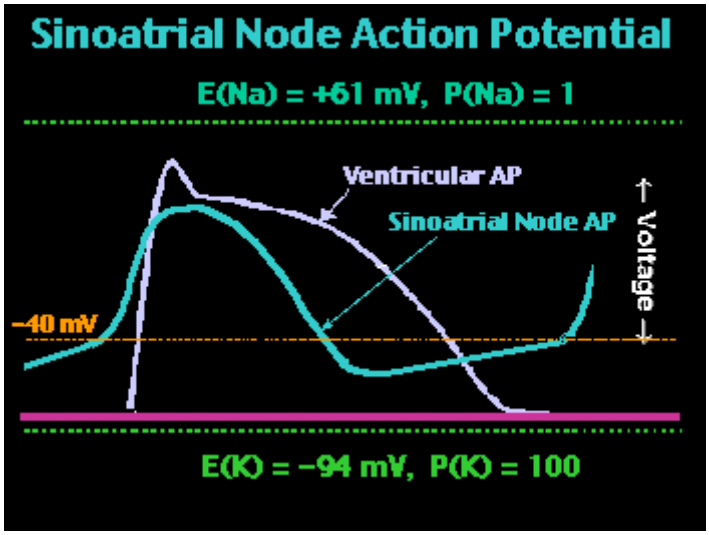

Figure 6: Sinoatrial and atrioventricular action potentials.

The pace set by SA node is regulated by antagonistic mechanisms: primarily through sympathetic innervations (release of NE, EPI – increases rate) and parasympathetic innervations (release of acetylcholine, lowers rate). These innervations act to regulate and control mean arterial pressure through heart rate, stroke volume, and through constriction and dilation of arterioles, arteries, and veins. This process is illustrated in figure 7 below.

[11] Ibid.

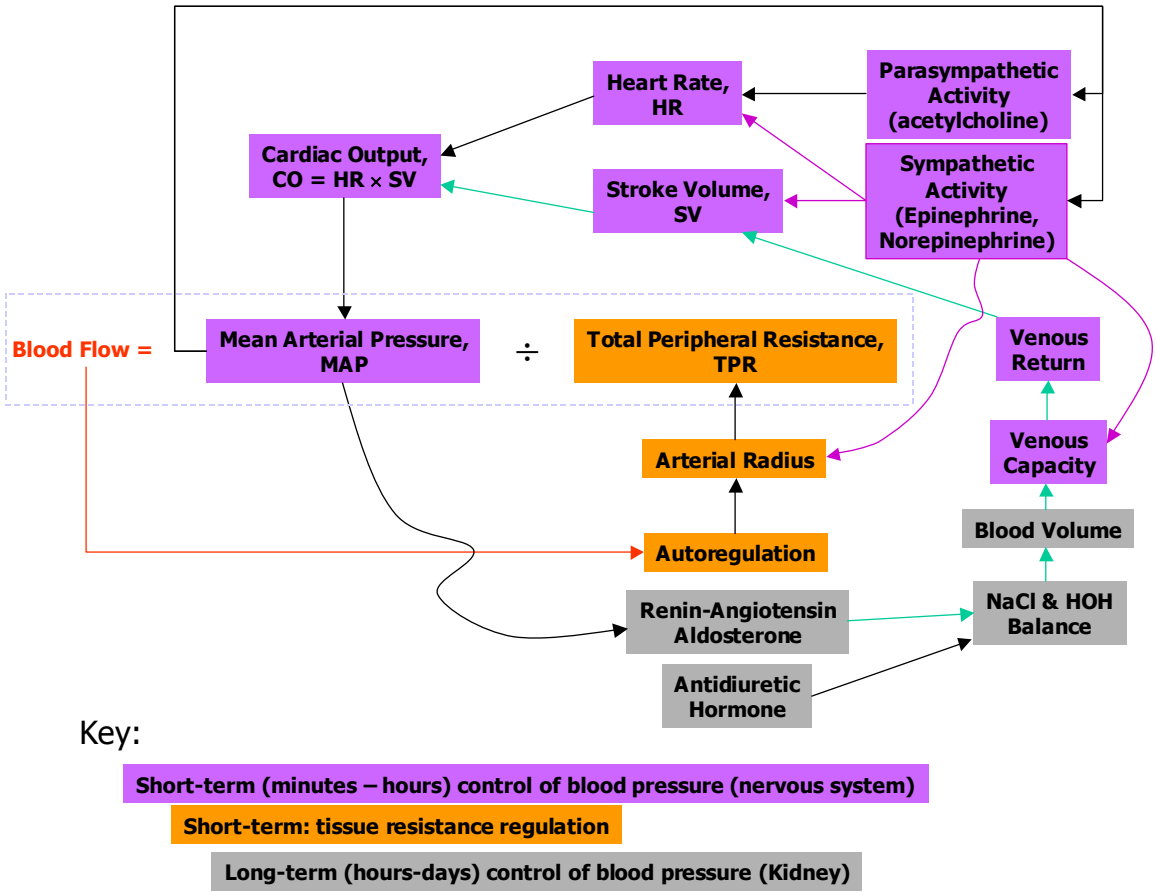

Figure 7: Circulatory system control diagram illustrating flow by which mean arterial pressure us maintained to accomplish required blood flow in body. (Drawing recreated by author)

Maintenance of the mean arterial pressure results with a concomitant relationship between cardiac output and total peripheral resistance. Normal cardiac output (L/min): ~ 5, with arterial pressure between ~75 and 160 mmHg), Cardiac output (L/min): 20-25 with right atrial pressure preload between 4 & 10 mmHg (maximum sympathetic stimulation); 10 – 15 with preload between 4 & 10 (normal sympathetic stimulation); 5-10 with 4 & 10 (parasympathetic stimulation).[12]

Measuring the amount of epinephrine in vivo and in vitro has been performed extensively.[13] One approach for doing so is cyclic voltammetry, details of which are available in the open literature.

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[12] Source: http://bio.bio.rpi.edu/Parsons/Universal%20Files/Lectures/L3VasFunction/3aLect.html (Accessed 8/23/02)

[13] Source: Adrenalin ELISA Kit Enzyme immunoassay users guide, IBL Hamburg, page 17.

Figure 8 is a diagram of the repetitive voltage waveform applied to an electrode for cyclic voltammetric detection of time dependent release (a). The solid line in (b) is the background current trace of the microelectrode with no analyte present. When an analyte (epinephrine) is present, a small observable current is seen overlaid on the background (dashed line in b). Subtracting the background trace from the signal trace yields a background subtracted cyclic voltammogram of epinephrine (c). Scan rate in this case was 300 V/sec every 100 msec"[14]

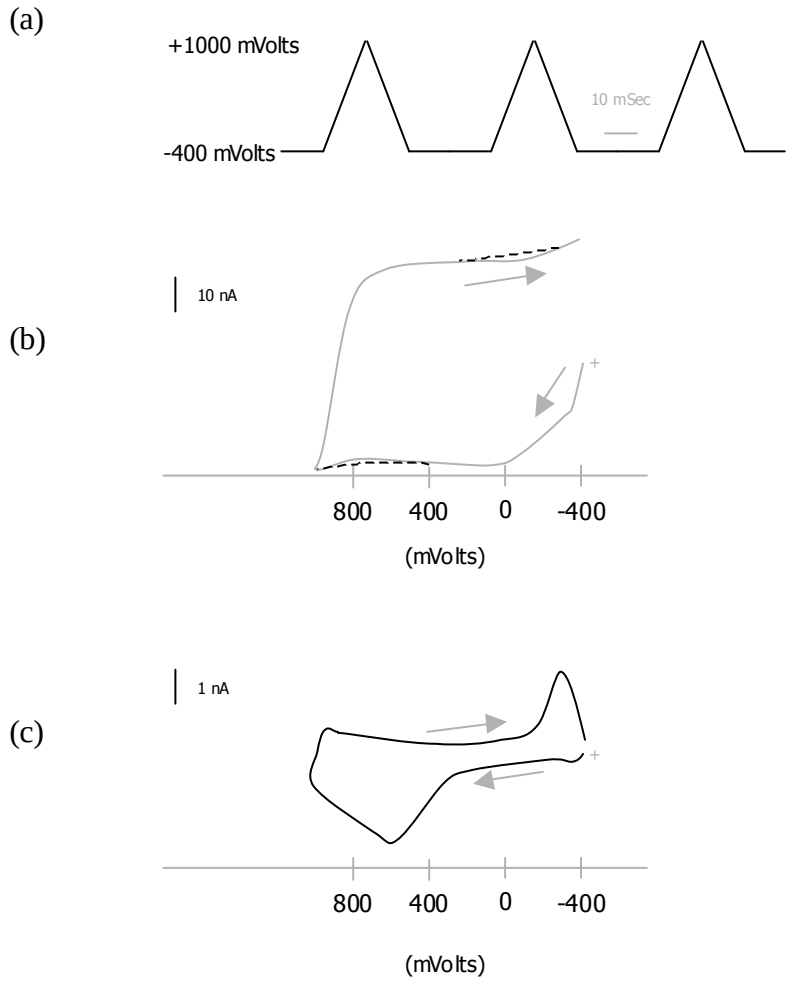

Figure 8: Diagram of the repetitive voltage waveform applied to an electrode for cyclic voltammetric detection of time dependent release. (Diagram recreated by author)

"The time necessary for diffusion to restore a uniform concentration of unoxidized dopamine near the electrode surface is approximately ten times the duration of electrolysis—approximately 20 msec in the example. To measure release from chromaffin cells in which the width at half-maximum of the current transient due to

[14] Ibid., page 16.

exocytosis is on the order of 100 msec—this scan interval is sufficient to quantitate the majority of release events. The maximum frequency of repetition of scans is the time required for the collapse of the depletion layer such that the next scan "sees" an unperturbed solution phase at the beginning of the scan. The depth of the depletion layer is approximated by:

> $\delta = \Delta_{red} t$, where δ is the depth of the depletion layer, Δ_{red} is the diffusion coefficient of unoxidized species, and t is the time in which oxidation is occurring."[15]

"For example, consider the oxidation of epinephrine at a scan rate of 800 V/sec as shown in figure 4. In the background-subtracted cyclic voltammogram the potential sweep begins at plus symbol. The oxidizing power of the electrode increases with positive-going potential and at approximately +400 mV oxidation of epinephrine begins – achieving a maximum at +650 mV. The oxidation current begins to decay thereafter because of depletion of unoxidized epinephrine at the electrode surface. After the maximum oxidation current, oxidation continues and the reaction rate at the electrode surface is limited by the diffusion of unoxidized epinephrine to the electrode surface. At +1000 mV the potential sweep direction is reversed. The potential is swept in a negative direction and the product that was generated by the forward scan is reduced back to its original form. The total time that oxidation occurs is related to the sweep rate and the time during which an oxidation current is produced. Because oxidation occurs over a range of 600 mV, we can divide this value by the sweep rate to determine total oxidation time. In this example, the total oxidation time is 2 msec The time necessary for diffusion to restore a uniform concentration of unoxidized dopamine near the electrode surface is approximately ten times the duration of electrolysis, or approximately 20 msec.

[15] Ibid., Page 16.

Details

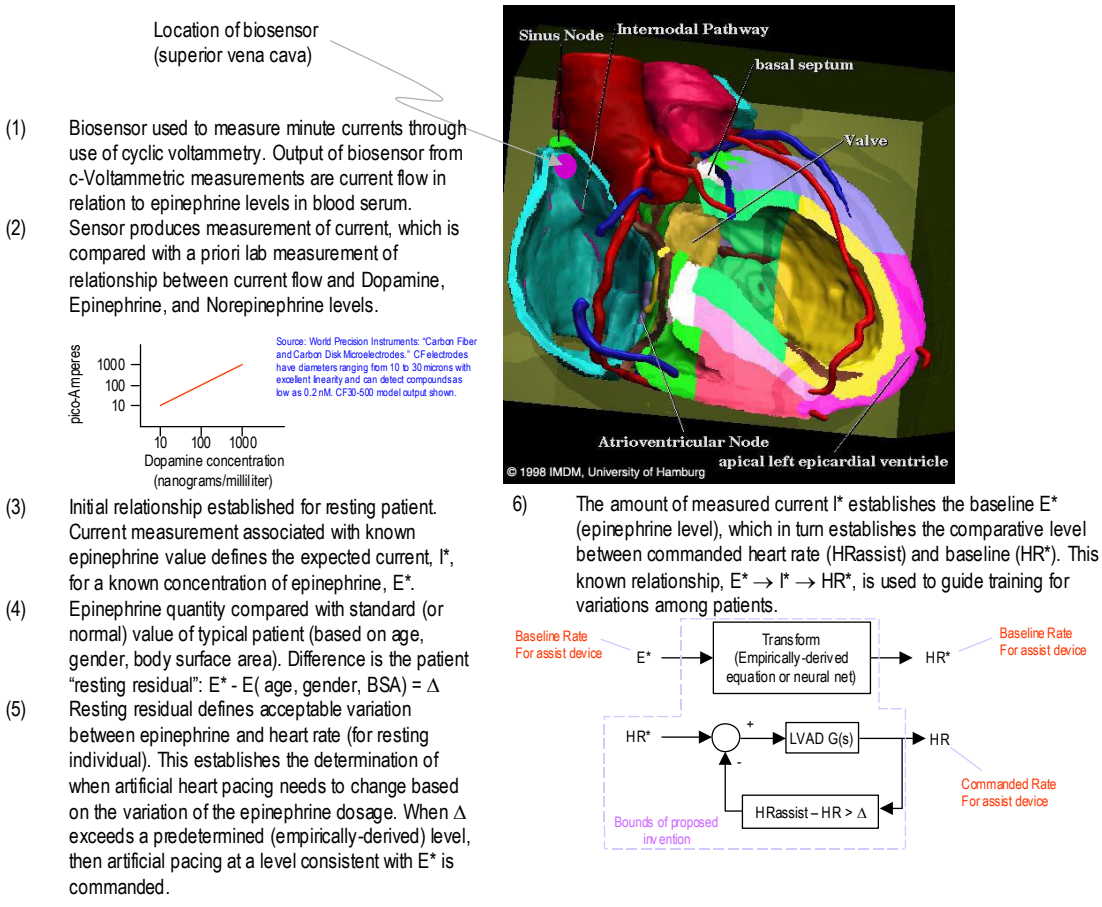

Figure 9: Overview of process steps involved in method for controlling action potential. (Diagram by author)

An overview of the process steps associated with the conceptual measurement and feedback control system is represented in the diagram of Figure 9. The method can be simply illustrated using the sample data beginning in Figure 10. Figure 10 shows an enlargement of the current-hormone diagram illustrated in the process steps (step 1) of Figure 9. The curve showing the relationship between anode current and Dopamine, Epinephrine, and Norepinephrine level is established based on a priori lab measurement data. This provides an "initial state" for determining patient specific response. Patient resting state illustrates the point at which a resting patient exists in terms of hormonal level and resulting anode current. In this case, it is shown to be coincident with a point on the a priori data curve (although this may not necessarily be the case).

Figure 11 shows the transformation from the anode current to the sinoatrial action potential rate (the heart rate) as a function of hormone level. The a priori model is drawn on this diagram to show the expected behavior.

Figure 12 illustrates a possible change in the heart rate of the patient as a function of the change in hormone level. The difference between the a priori model and the actual heart rate at a specific hormone level is shown as the difference, Δ. An increase in this difference above a specified user threshold level establishes the point at which a change in mechanical pacing shall take place.

The a priori curve establishes expected performance for early patient training. As the patient experiences more events, a resulting set of data become available that define the patient's tailored response to changes in sympathetic and parasympathetic stimulation levels. This is illustrated notionally in figure 13.

As the patient begins to build a training set, a new relationship can be established for this patient (separate from the a priori relationship).

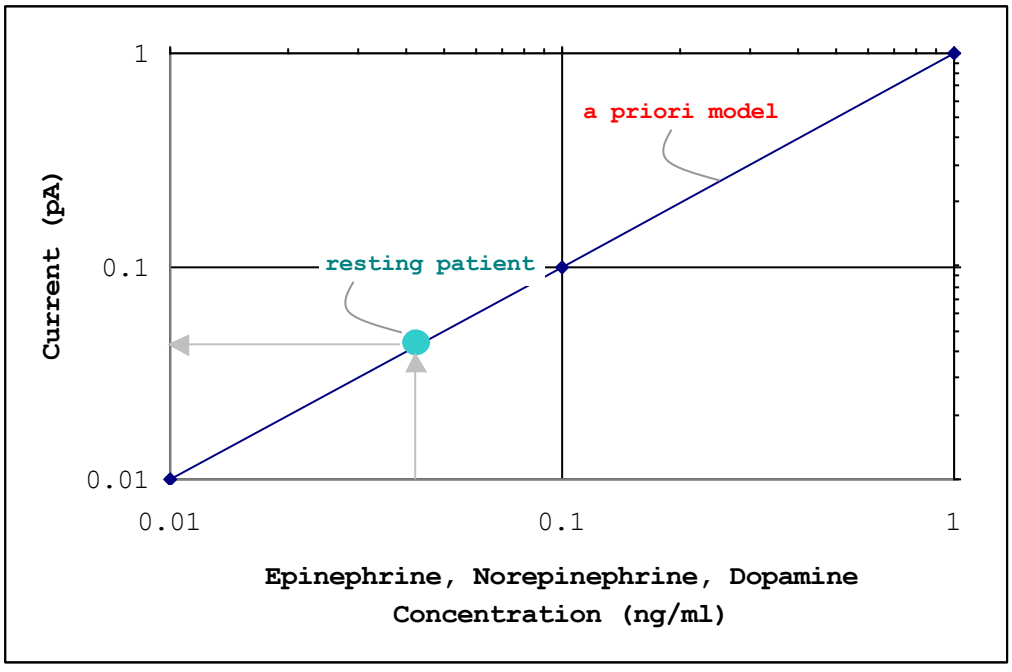

Figure 10: Resting and a priori anode current determined from cyclic voltammetry versus hormone level. (Plot by author)

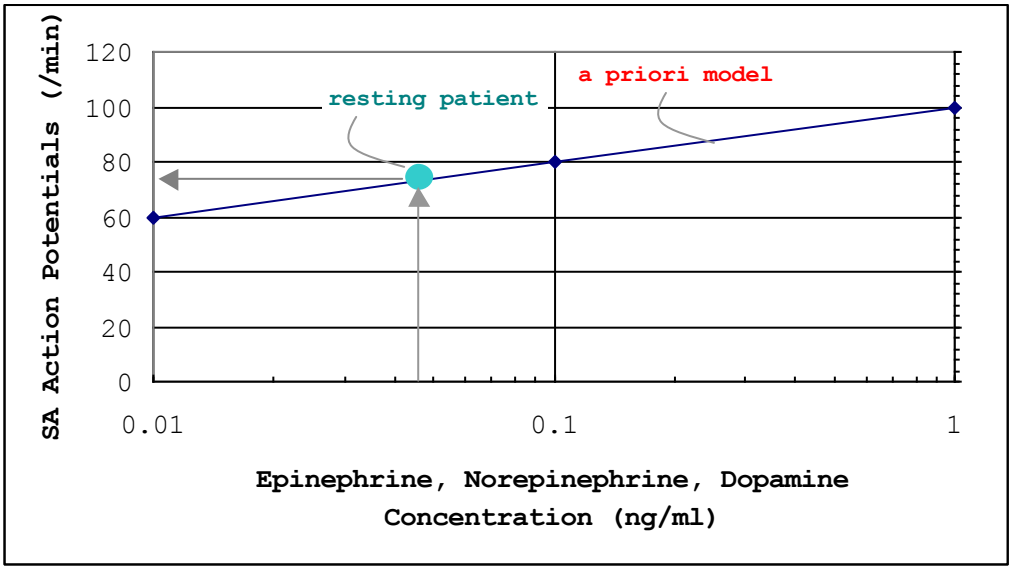

Figure 11: Resting sinoatrial action potential rate. (Plot by author)

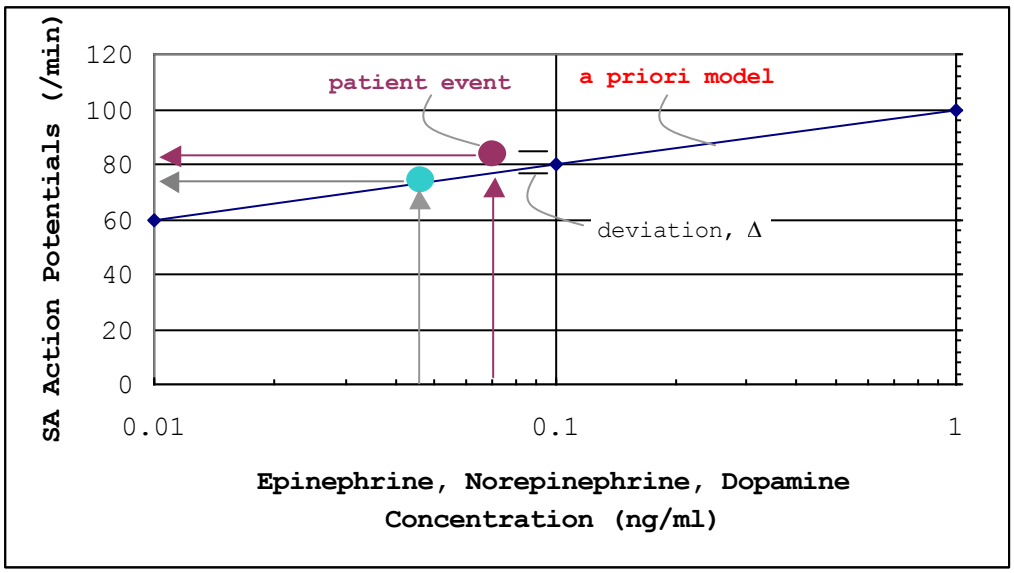

Figure 12: Patient event-based change in SA Action potential rate. (Plot by author)

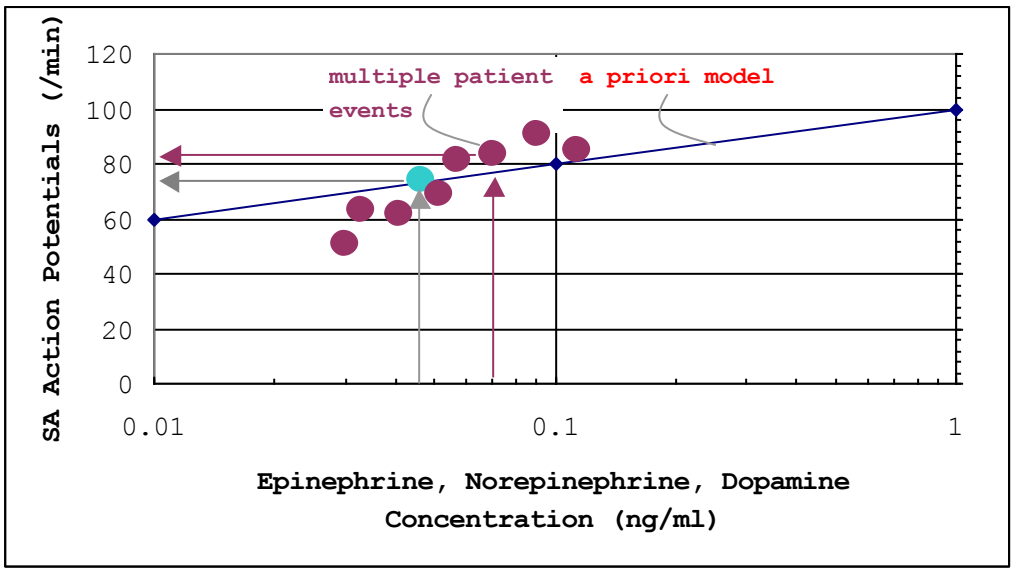

Figure 13: Multiple patient events and relationship to a priori data. (Plot by author)

This new pacing relationship can be maintained for this specific patient within the pacing unit as a mathematical equation—or regression fit—associated with the tailored response of this particular patient. The trained relationship then establishes the expected behavior for an assist device. The equation relating pacing to hormone level can be stored in an electronic patient record (for instance) for recall, updated training, or for use in data mining to compare and develop more complex relationships with those of other patients. The regression fit is shown in Figure 14.

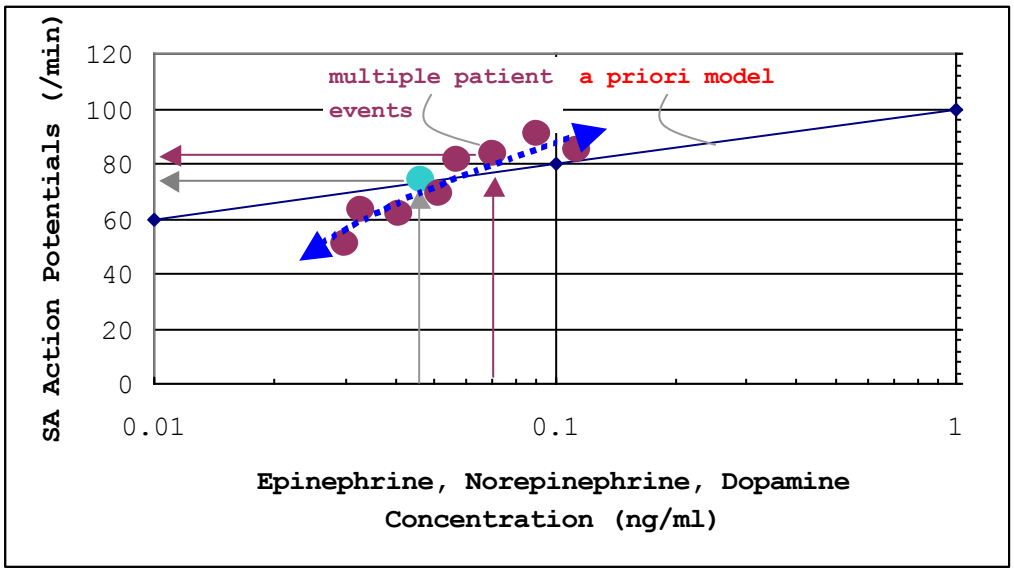

Figure 14: Sinoatrial pacing regression relationship for a specific patient. (Plot by author)