Technical Appendix

Here we present more details needed for the technical appendix.

A Real-Time Requirements of Pacemakers

An electrocardiogram (ECG) is a noninvasive procedure that measures and records the electrical activity (voltage versus time) of the heart. This section introduces a graphical representation for the heart-pacemaker closed-loop system using a combined ECG graph and a so-called pacemaker timing ladder diagram. After explaining how to read these diagrams in the first subsection, we showcase two crucial scenarios of the pacemaker. We validate the DC specifications for the DDD pacemaker using these requirements in Section 5.1.

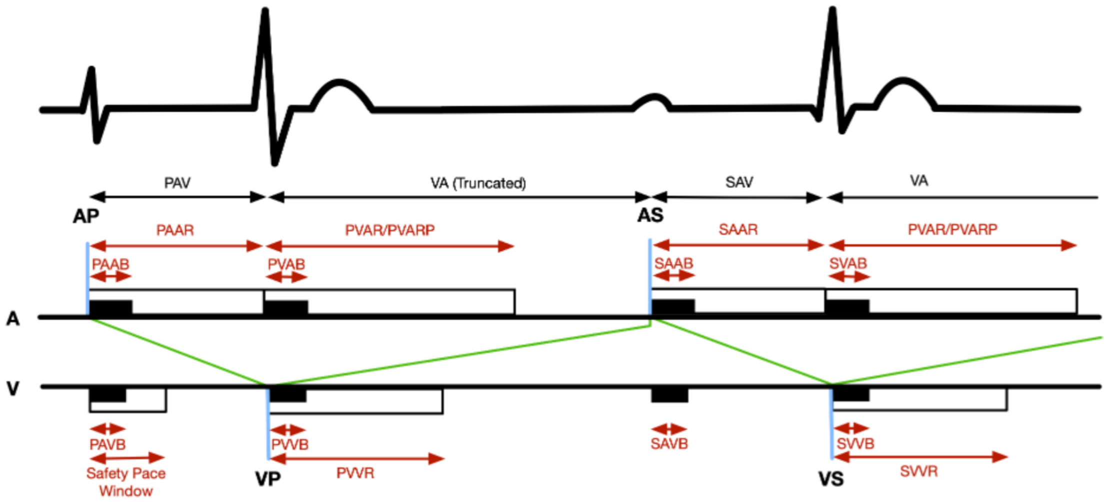

Figure 7: An ECG (top) and pacemaker timing ladder diagram (bottom) showing two cardiac cycles. The first cycle represents a paced atrial and ventricular events (AP,VP) in the ladder diagram. The second cycle represents intrinsic heart rhythm with atrial and ventricular sensed events (AS,VS). The post VP VA interval has been truncated by the early AS arrival.

A.1 ECG and the Timing Ladder Diagram

The waveform at the top of Figure 7 is a simple representation of heart activity as seen in a surface ECG. The waveform begins with the pacemaker delivering pacing pulses to the atrium and ventricle. Pacing activity is recognized by the sharp signal spikes that extend well above and below baseline followed by the T-wave, a large hump in the ECG waveform. This is followed by intrinsic paces by the heart of the two chambers, again followed by the ventricular refractory T-wave. The ladder diagram at the bottom of Figure 7 depicts how a pacemaker views the timing relations between cardiac activity.

The AV and VA intervals. The top and bottom horizontal black lines represent timing activities in the atrium and ventricle, respectively. Cardiac events are represented by vertical lines and labeled with a two letter acronym where the first letter represents the event chamber: A(trium) or V(entricle) and the second is the event: S(ense) or P(ace). An atrial sense would have the label AS. The cardiac cycle is measured from atrial event to atrial event and is broken into two halves: *the AV interval* (the time from the atrial event to the ventricular event) and *the VA interval* (the remainder of the cardiac cycle from the ventricular event to the next atrial event). The AV interval can be further identified as a sensed (SAV) or paced (PAV) interval based on the event that triggered it. These intervals are displayed at the top of the ladder diagram and are synchronized with ECG.

Blanking and Refractory Periods. Each interval has four timing periods that start coincident with the event that began the interval. The *blanking periods* provide noise rejection immediately after a cardiac event and all cardiac activity is ignored during this time. *Refractory periods* represent the time required for the heart chamber to recover from the event. While these are considered valid cardiac signals, they occur too soon in the cardiac cycle. These periods are given a four letter acronym where the first letter denotes the event type (S/P), the second is the chamber of the event (A/V), the third is the chamber of the timer (A/V), and the fourth is the type of the period (B/R).

The atrial blanking period following a sensed ventricular event would be SVAB. Following a ventricular event, an atrial blanking period (PVAB/SVAB) and refractory period (PVAR/SVAR) will begin along with similar periods in the ventricle (PVVB/PVVR). Similar periods occur after an atrial event. There are a few exceptions. By tradition, atrial sensed and paced refractory periods following a ventricular event are referred to as PVAR. There is no ventricular refractory period after an atrial

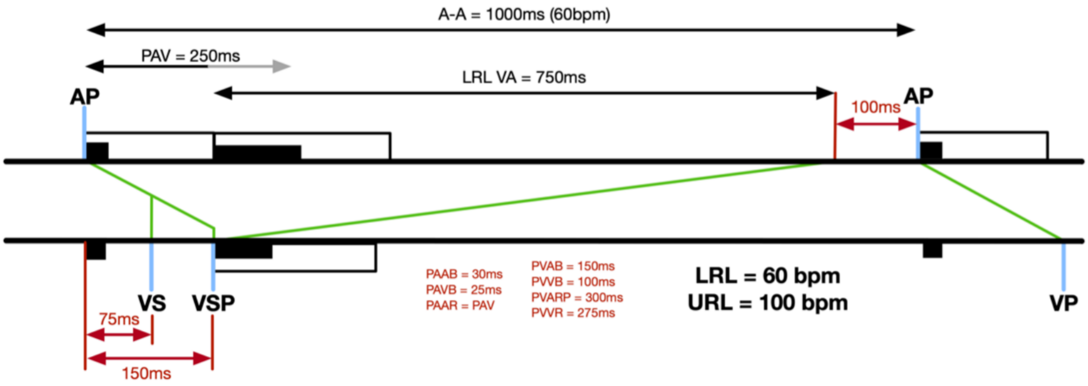

Figure 8: Safety Pacing and Atrial Holdoff

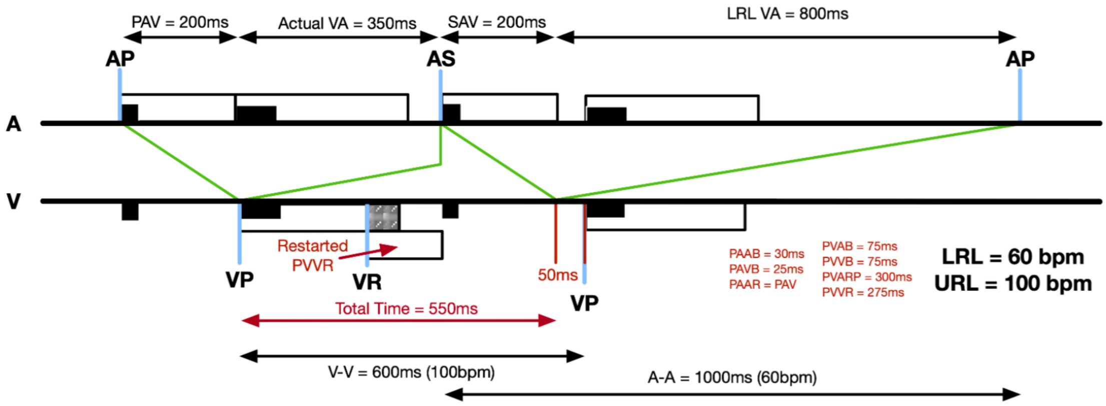

Figure 9: Upper Rate Holdoff and Ventricular Refractory Sensed Event

event. Instead, a safety pace period may exist. If a ventricular sensed event occurs during the safety pace window, a back up or safety pace is generated at the end of the window to provide additional hemodynamic support (see Example A.2).

The green line in the diagram shows the progressing of the interval time. It starts at the event on the timeline of the chamber where it occurred. If it reaches the opposite timeline without an intrinsic cardiac event, a pace in the chamber associated with the reached timeline is generated. The following scenarios graphically explain two key requirements.

A.2 Safety Pacing and Atrial Holdoff

Requirement. *In absence of intrinsic atrial activity, the pacemaker attempts to maintain the time between atrial beats at the Lower Rate Limit (LRL).*

Example. In Figure 8, the lower rate is 60 bpm (1000ms). A ventricular sensed event was detected at 75ms after the atrial pace. This VS falls into the safety pace period. The PAV interval continues as indicated by the green line until the safety pace window closes when a ventricular backup pace occurs 150ms after the atrial pace and the VA interval begins. At the end of the VA interval, the next atrial pace must be held off. A pace at the completion of the VA interval would occur 100ms too soon because of the back pace shortened PAV interval and would result in a pacing rate faster than lower limit. The atrial pace ultimately occurs 1000ms after the last atrial pace maintaining the A-A timing of the LRL.

A.3 Upper Rate Holdoff and Ventricular Refractory Sense

Requirement. *A pacemaker must never pace above the Upper Rate Limit (URL).*

Example. In Figure 9, the example shows two conditions that needs to be address by the pacemaker. Here, the cardiac cycle begins with complete pacing support with an AP followed by a VP at the conclusion of the PAV interval (200ms). A sensed ventricular event occurs at 250ms. The PVVR period is still active so this event is labeled a refractory ventricular sense (VR). The PVVR timer is restarted to allow for ventricular repolarization to complete after the VR but the overall VA interval is not

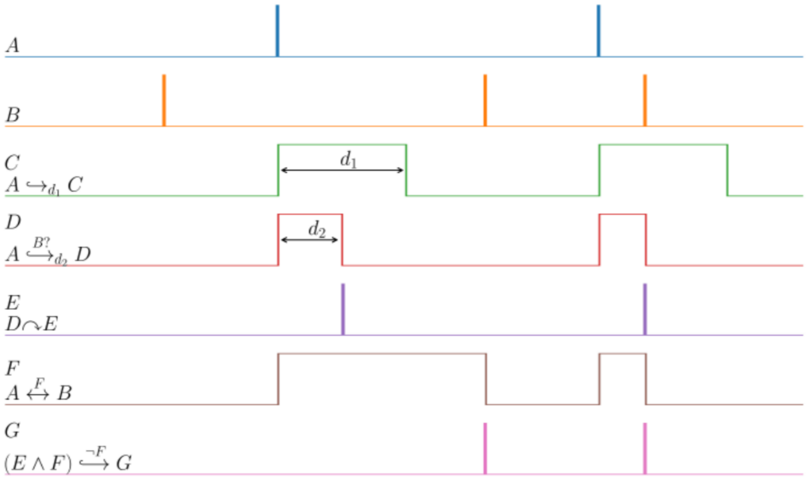

Figure 10: A visual explanation of the derived operators.

affected. An atrial sense occurs at 350ms after the VP. Being outside of PVAR, this is a valid atrial event and the AV interval begins. At the completion of the AV interval, 550ms have passed since the VP while the URL is 600ms. The VP must be held off for 50ms to prevent violation of the URL requirement. The VA interval still starts at the end of the AV interval to maintain the LRL rate of 1000ms. If the AV interval was also held off until the VP, the next atrial pace would occur at 1050ms, a violation of LRL.

B DC Specifications for Pacemakers

Now we are in a position to present the DC specifications for the DDD pacemaker requirements from (Laboratory 2007). We start this section by introducing some derived operators of DC that allow us to succinctly express various idioms in pacemaker specifications. In Section B.2 we introduce various signals and terms used in our specifications, while in Section B.3, we use these operators and signals to express DDD requirements.

B.1 Derived Operators: Syntactic Sugar for DC

We present some derived DC operators that allow us to express our specifications more succinctly.

1. We extend the usage of $\lceil X\rceil^\bullet$ and $\lceil X\rceil$ over Boolean combination of predicates as follows.

$$\lceil X\otimes Y\rceil^\bullet \stackrel{\text{def}}{=} \lceil X\rceil^\bullet \otimes \lceil Y\rceil^\bullet, \quad \lceil \neg X\rceil^\bullet \stackrel{\text{def}}{=} \neg\lceil Y\rceil^\bullet, \quad \lceil X\rceil \stackrel{\text{def}}{=} \Box(\lceil X\rceil^{\bullet\frown}\mathsf{true}), \quad \text{and} \quad \lceil X\rceil^d \stackrel{\text{def}}{=} (\ell{=}d\wedge\lceil X\rceil)^\frown\mathsf{true}$$

where $\otimes$ is some logical binary operator and X and Y are Boolean formulae over predicates.

2. The operator $A \hookrightarrow_d B$ encodes that A triggers B for precisely d time units if A occurs again before d time then B is re-triggers, i.e.,

$$A \hookrightarrow_d B \stackrel{\text{def}}{=} \Box\Big((\ell\ge d+1)\wedge(\lceil A\rceil^{\bullet\frown}\mathsf{true})\Rightarrow(\ell=1)^\frown\lceil B\rceil^d\Big)\wedge\Box\Big((\ell\ge d+1)\wedge\lceil\neg A\rceil^d\Rightarrow \ell{=}d+1^\frown\lceil\neg B\rceil^{\bullet\frown}\mathsf{true}\Big)$$

3. The operator $A\overset{C}{\leftrightarrow}B$ encodes that C holds between events A and B, i.e.,

$$A\overset{C}{\leftrightarrow}B \stackrel{\text{def}}{=} \Box(\ell\ge1\wedge(\lceil A\wedge\neg B\rceil^{\bullet\frown} true)\Rightarrow(\ell{=}1^\frown waitFor(B,C)))\wedge\Box(\ell\ge1\wedge(\lceil B\rceil^{\bullet\frown} true)\Rightarrow(\ell{=}1^\frown waitFor(A,\neg C)))$$

where $waitFor$ is defined as follows.

$$waitFor(X,Y)\stackrel{\text{def}}{=}\lceil\neg X\wedge Y\rceil\vee(\lceil\neg X\wedge Y\rceil^\frown\ell{=}1^\frown\lceil X\wedge Y\rceil^{\bullet\frown} true)\vee(\lceil X\wedge Y\rceil^{\bullet\frown} true)$$

4. The operator $A\curvearrowright B$ encodes that B is true when A transitions from true to false, i.e.,

$$A\curvearrowright B\stackrel{\text{def}}{=}\Box\big(\lceil A\rceil^{\bullet\frown}(\ell=1)^\frown\lceil\neg A\rceil^\bullet\Leftrightarrow(\ell=1)^\frown\lceil B\rceil^\bullet\big)^\frown true.$$

5. Operator $A\xhookrightarrow{B?}_d C$ encodes C will be true after A and turns false after either a delay of time d or arrival of B,

$$A\xhookrightarrow{B?}_d C \stackrel{\text{def}}{=} (A\hookrightarrow_d X)\wedge(A\overset{Y}{\leftrightarrow}B)\wedge\lceil(X\wedge Y)\Leftrightarrow C\rceil$$

where X and Y are intermediate signals.

6. Operator $(A \wedge B) \xhookrightarrow{\neg B} C$ encodes that C will be true when B turns false after both A and B are true,

$$(A \wedge B) \xhookrightarrow{\neg B} C \overset{\text{def}}{=} (B \curvearrowright X) \wedge (A \wedge B \overset{Y}{\leftrightarrow} X) \wedge (Y \curvearrowright C)$$

where X and Y are intermediate signals.

B.2 Signals, Time Intervals, and Derived Signals

Our specifications interpret DC formulae over signals therefore we express the specifications with the help of signals. In this modelling, we follow the convention that signal variable names are given in capital letters. A pacemaker receives the "sensing events" as input, while outputs the "pacing events." Depending on the real-time constraints enforced by the requirements, the pacemaker decides whether it is appropriate to produce a pace signal at any given time instant. The time constraints are encoded with the help of derived signals. We first describe the input and outputs signals and then present the derived signals with their intuitive interpretations.

Input and output signals. The VS (ventricular sense) and AS (atrial sense) signals denote the heart activity sensed in the ventricle and atrium respectively. The output pacing signals of the ventricle and atrium are VP and AP. Using the sensed signals as input, the pacemaker decides when to produce VP and AP. We express the conditions that either enable or inhibit the pacing signals using derived signals that depend on the input and output signals.

Time interval constants. The following time constants define various configurable intervals of a pacemaker. We write them in lowercase letters. We will use them to define derived signals and write specifications.

- The `lrl` (lower rate limit) interval is the longest allowed time between two consecutive paced or ventricular sensed events, while the `url` (upper rate limit) interval is the shortest time possible between two consecutive ventricular paced or sensed events.
- The `pav` (paced atrium-ventricle) and `sav` (sensed atrium-ventricle) intervals start from a paced atrial event and sensed atrial event, respectively.
- The `va` (ventricle-atrial) interval starts after each non-refractory VS or after the expiration of `pav` or `sav`.
- The `pvab`, `pavb`, `pvvb`, `paab`, `svab`, `savb`, `svvb` and `saab` (paced/sensed ventricular/atrial atrial/ventricular blanking) intervals start at paced/sensed events at their second letter and affect the events in the third letter.
- The `pvvr`, `pvar`, `paar`, `svvr`, `svar` and `saar` (paced/sensed ventricular/atrial atrial/ventricular refractory) intervals are defined in an analogous fashion to the previous item.
- `safe` interval is used in case of enabling of safety ventricular pacing.

Derived signals. We present the derived signals that we need to write the specifications. We have divided the derived signals depending on the signals and timing information used for the construction of the signals.

- **Refractory and blanking signals.** For each paced or sensed (P or S) events in each chamber (A or V), we need to keep track of refractory or blanking (R or B) intervals that may affect any of the chambers (again A or V). Using the four letters, we describe 16 signals in writing our specification. For example, signal $PVVR$ is true for `pvvr` period after a paced ventricular event. We will not use two of the sixteen, namely $SAVR$ and $PAVR$, since they have no biological significance. In some circumstances, we need extended $PVAR$ for which we used signal $ExPVAR$.
- **Accepted/non-ignored and non-refractory sensed signals.** The sensed events are sometimes masked. To achieve modularity, we define four signals VSA, ASA, VSN, and ASN, when each sensed events (V or A) are not masked by blanking or refractory period (A or N).
- **AV/VA interval signals.** If sufficient time has been passed since last paced or sensed (P or S) atrial event then we schedule a ventricular pace event if no other condition inhibits. We use either of two signals PAV and SAV to indicate the state of the interval depending on the event triggering the interval. We use signal VA to indicate the similar timing requirement from ventricular event to atrial pace event. For the VA interval, the specification does not differentiate between paced and sensed events in starting the interval. We also define signals $EPAV$, $ESAV$ and EVA to indicate the 1 to 0 transitions in PAV, SAV and VA respectively.
- **Pacing time delay signals.** We use LRL and URL signals to indicate the lower and upper limit of pacing delays.
- **Different ventricular pacing signals.** There are different types of ventricular pace signals `scheduledVP`, `lateVP` and `safeVP` that are triggered in different circumstances. These signals together contribute to the final output ventricular pace (VP) signal.
- **Some special signals.** The signal $BOOT$ is used as a trigger to start the system. Signal $NoAS$ represents the absence of atrial sense after a non-refractory ventricular sensed event until an ASA event is seen.
- **Signals for permissive pacing.** The signal VO is input to our system along with the AS and VS signal to allow pacing decision from the reinforcement learning agent. The signal $Vother$ is used to allow permissive pacing using the reinforcement learning agents input to our system.

B.3 Pacemaker Specifications

We divide our specifications in the following two groups. The first group defines the signals and delays which will be used further in writing the specifications. In the second group, we use the defined signals to write specification of the pacemaker.

1. The BOOT signal marks the start of the pacemaker.

$$\lceil BOOT \rceil^{\bullet} \vee \lceil BOOT \rceil^{\bullet} {}^\frown \ell = 1 {}^\frown \lceil \neg BOOT \rceil$$

2. A ventricular blanking period shall start immediately after a ventricular/atrial paced or sensed event. The blanking intervals `pvvb`,`svvb`,`pavb`,`savb` are relevant to ventricular events.

$$(VP \hookrightarrow_{\texttt{pvvb}} PVVB) \wedge (AP \hookrightarrow_{\texttt{pavb}} PAVB) \wedge (VSA \hookrightarrow_{\texttt{svvb}} SVVB) \wedge (ASA \hookrightarrow_{\texttt{savb}} SAVB)$$

3. During the post atrial event, ventricular blanking period (PAVB/SAVB), ventricular sensed events shall be ignored. During the post ventricular event, ventricular blanking period (PVVB/SVVB), ventricular sensed events shall be ignored.

$$\lceil VS \wedge \neg PVVB \wedge \neg PAVB \wedge \neg SVVB \wedge \neg SAVB \Leftrightarrow VSA \rceil$$

4. An atrial blanking period shall start immediately after a atrial/ventricular paced or sensed event. `paab`,`saab`,`pvab`,`svab` are the blanking intervals relevant to atrial events.

$$(VP \hookrightarrow_{\texttt{pvab}} PVAB) \wedge (AP \hookrightarrow_{\texttt{paab}} PAAB) \wedge (VSA \hookrightarrow_{\texttt{svab}} SVAB) \wedge (ASA \hookrightarrow_{\texttt{saab}} SAAB)$$

5. During the post atrial event, atrial blanking period (PAAB/SAAB), atrial sensed events shall be ignored. During the post ventricular event atrial blanking period (PVAB/SVAB), atrial sensed events shall be ignored.

$$\lceil AS \wedge \neg PVAB \wedge \neg PAAB \wedge \neg SVAB \wedge \neg SAAB \Leftrightarrow ASA \rceil$$

6. A post ventricular, atrial refractory period (PVAR) and post ventricular, ventricular refractory period (PVVR) shall start immediately after a non-refractory ventricular sensed or paced event.

$$((VP \vee VSA) \hookrightarrow_{pvvr} PVVR) \wedge ((VP \vee VSN \vee (ASA \wedge PVAR)) \hookrightarrow_{\texttt{pvar}} PVAR)$$

7. A ventricular sensed event is non-refractory if it occurs when PVVR is not true.

$$\lceil \neg PVVR \wedge VSA \Leftrightarrow VSN \rceil$$

8. A post atrial, atrial refractory period (PAAR) shall start immediately after a non-refractory atrial sensed or paced event. Note that the PAAR/SAAR runs the entire length of the PAV/SAV interval.

$$(AP \vee ASN) \xleftrightarrow{PAAR} (VP \vee VSN)$$

9. Atrial refractory runs the entire AV interval.

$$\lceil \neg PAAR \wedge \neg PVAR \wedge \neg ExPVAR \wedge ASA \Leftrightarrow ASN \rceil$$

10. A fixed paced AV (PAV) delay shall be initiated by a paced atrial event. A fixed sensed AV (SAV) delay shall be initiated by a sensed non-refractory atrial event. EPAV and ESAV signals mark the end point of the AV interval.

$$\lceil VSN \Leftrightarrow Vother \rceil$$
$$(AP \xhookrightarrow{Vother?}_{\texttt{pav}} PAV) \wedge (ASN \xhookrightarrow{Vother?}_{\texttt{sav}} SAV) \wedge$$
$$\big((PAV \wedge \neg Vother) \curvearrowright EPAV\big) \wedge \big((SAV \wedge \neg Vother) \curvearrowright ESAV\big)$$

Please note that we have introduced a signal $Vother$, which is synonym of VSN. We need this signal to be able to adapt our specification to support learning agent later in section B.4.

11. A fixed VA delay shall be initiated after each non-refractory sensed ventricular event or after completion of the AV (SAV/-PAV) interval, whichever occurs first.

$$(Vother \vee ESAV \vee EPAV \vee BOOT) \xhookrightarrow{ASN?}_{\texttt{va}} VA \wedge ((VA \wedge \neg ASN) \curvearrowright EVA)$$

12. A non-refractory ventricular sensed event followed by a second non-refractory ventricular event without an intervening atrial sensed event (a premature ventricular contraction or PVC) shall start an extended PVAR.

$$(VSN \xleftrightarrow{NoAS} ASA) \wedge ((NoAS \wedge VSN) \hookrightarrow_{\texttt{expvar}} ExPVAR)$$

13. The LRL and URL interval starts at a paced ventricular event or non-refractory ventricular sensed event.

$$((VP \vee VSN) \hookrightarrow_{\texttt{lrl}} LRL) \wedge ((VP \vee VSN) \hookrightarrow_{\texttt{url}} URL) \wedge ((AP \vee ASN) \hookrightarrow_{\texttt{lrl}} ALRL) \wedge ((AP \vee ASN) \hookrightarrow_{\texttt{url}} AURL)$$

Specifications AP1-AP4 are for generating AP events and VP1-VP4 are for generating VP events. OE1 and OE2 define the operation envelop of a pacemaker.

- **[AP1]** VRP extension beyond the VA interval shall cause the atrium to be paced at the completion of the VA interval (noise reversion). *This condition does not add any restriction. Therefore, we do not need a formula.*
- **[AP2]** Ventricular sensed events outside of SVVR/PVVR shall begin a new VA interval. *This condition does not add any restriction. The definition of VA already handles the extension.*
- **[AP3]** Atrial sensed events inside of PVAR shall not start the SAV interval nor inhibit the scheduled atrial pace. Atrial sensed events outside of PVAR shall begin an SAV interval. *This condition does not add any restriction. The definition of VA already handles the end of VA.*
- **[AP4]** An atrial paced event shall occur upon completion of VA.

$$\lceil (EVA \wedge \neg ASN \wedge \neg AURL) \Leftrightarrow scheduledAP \rceil$$

- **[AP5]** If VA periods ends and URL timing has not met, the AP will wait for URL to be over.

$$((EVA \wedge \neg ASN) \wedge AURL) \xhookrightarrow{\neg AURL} lateAP, \qquad \lceil (scheduledAP \vee lateAP) \Leftrightarrow AP \rceil$$

- **[VP1]** A non-refractory ventricular sensed event during the AV interval *outside the safety period* shall begin a VA interval. *This condition does not add any restriction. The definition of PAV/SAV already handles the end of PAV/SAV.*
- **[VP2]** A ventricular paced event shall occur upon completion of AV interval unless the upper rate limit has not been met.

$$\lceil ((EPAV \vee ESAV) \wedge \neg VSN \wedge \neg URL) \Leftrightarrow scheduledVP \rceil$$

- **[VP3]** If AV periods ends and URL timing has not met, the VP will wait for URL to be over.

$$(((EPAV \vee ESAV) \wedge \neg Vother) \wedge URL) \xhookrightarrow{\neg URL} lateVP$$

- **[VP4]** A non-refractory ventricular sensed event during PAV interval inside safety period shall cause the next scheduled ventricular pace to occur at safety pace time.

$$(AP \hookrightarrow_{\texttt{safe}} SAFE) \wedge (VSN \wedge SAFE) \xhookrightarrow{\neg SAFE} safeVP, \qquad \lceil (scheduledVP \vee lateVP \vee safeVP) \Leftrightarrow VP \rceil$$

- **[OE1]** The time between paces shall not exceed the lower rate limit interval (LRL).

$$\lceil VP \Rightarrow LRL \rceil$$

- **[OE2]** The time between a ventricular event and the next ventricular pace shall not be less than the Upper Rate Limit (URL) interval.

$$\lceil VP \Rightarrow \neg URL \rceil$$

This completes the set of requirements for DDD pacemaker from (Laboratory 2007). ■

B.4 Permissive Specification

To support the inputs from the learning agent, we introduce another input signal VO that indicates the pacing decision of the learning agent. We allow learning agent to interrupt PAV or SAV, when $SAFE$ and URL signals are false. To accodate VO, we modify the definition of $Vother$.

$$\lceil VSN \vee (VO \wedge \neg SAFE \wedge \neg URL) \Leftrightarrow Vother \rceil$$

The specification VP2 ensures that if the PAV or SAV intervals are ended by VO then we produce a $scheduledVP$, i.e., the learning agent is allowed to pace.