SUPPLEMENTARY MATERIAL

Contents

APPENDIX-I: List of Select AP Platforms

Supplementary Table 1. List of select AP platforms developed in academic settings which have been used in regulated clinical research studies. For each system, we report the reference publication, platform and its operating system (OS) used, supported CGM and pump devices and integration of full-featured remote monitoring in the system for clinical study.

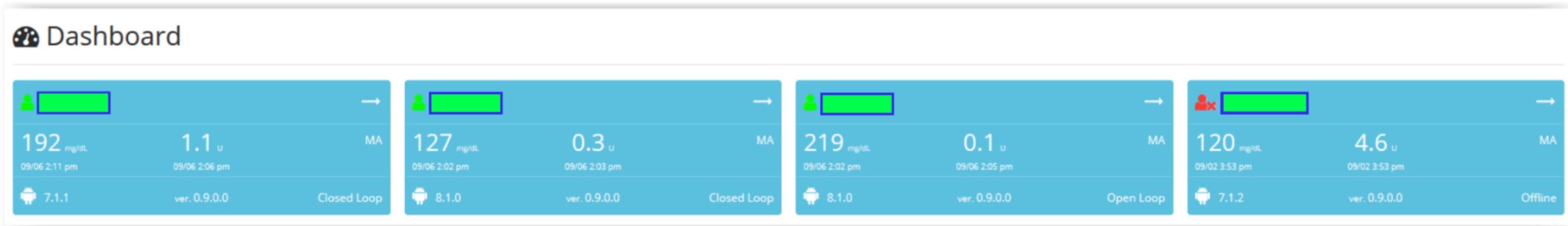
#	System	Ref. in main text	Platform	Platform OS	CGM Devices	Pump Devices	Remote Monitoring
1	DiAs	9	smartphone	Android	Dexcom G4	Roche Accu-Chek/ Tandem t:AP	Yes
2	FlorenceD2A/M	12	smartphone	Android	FreeStyle Navigator II/ Medtronic Enlite 3	Dana R Diabecare/ Medtronic 640G	No
3	Bionic AP	11	smartphone	iOS	Dexcom G4	Tandem t:AP	Yes
4	OHSU Bihormonal AP	14	smartphone	Android	Dexcom G5	Tandem t:AP	Yes
5	BiAP	13	microchip/ smartphone	Not applicable/iOS	Dexcom G5	Tandem t:AP	Yes
6	APS/pAPS	10	laptop/ tablet	Windows	FreeStyle Navigator/ Dexcom STS7/G4	Insulet Omnipod/ Animas OneTouch Ping	No
7	iAPS	-	unlocked smartphone	Android/ iOS	Dexcom G5/G6	Tandem t:AP/ Insulet Omnipod	Yes

APPENDIX-II: Remote Monitoring (RM)

Authorized individuals can utilize the secure iAPS Remote Monitoring (RM) website portal to track the user's glycemic status. Data becomes visible on the portal as it streamed to the cloud from the app running on a smartphone connected to the internet. The portal can be accessed from modern browsers running on a desktop, laptop, or phone.

It is worth mentioning that the iAPS system can seamlessly stream its data to the cloud despite the phones not always being in range of a Wi-Fi signal, without requiring any action on the part of the subject. The preferred method of phone connection to the internet is via a Wi-Fi connection, however, the app can also accommodate connection via a cellular network if the phone is configured to allow switching between Wi-Fi and cellular networks. The app will also operate when wholly disconnected from the internet, queuing data locally until an internet connection is re-established, whereupon it will push the queued data to the cloud.

For the purpose of illustration of RM features, we have utilized simulated data and simulated alarms generated during the system testing, and hence it is not related to the reported clinical study.



Supplementary Figure 1. The main dashboard of iAPS Remote Monitoring (RM) portal.

Upon login, the dashboard shows a snapshot of all subjects (in this case testers) currently in the system with salient information such as current CGM with timestamp and its trend, last delivered bolus with timestamp, current version of the iAPS, the smartphone platform running the app (in this case is the Android OS) and status of the system (Closed-loop, Open-loop or Offline) as shown in Supplementary Figure 1.

Upon clicking any of the subject on the dashboard, the user is taken to a subject-specific main page. For each subject, the main page has the following sub-pages:

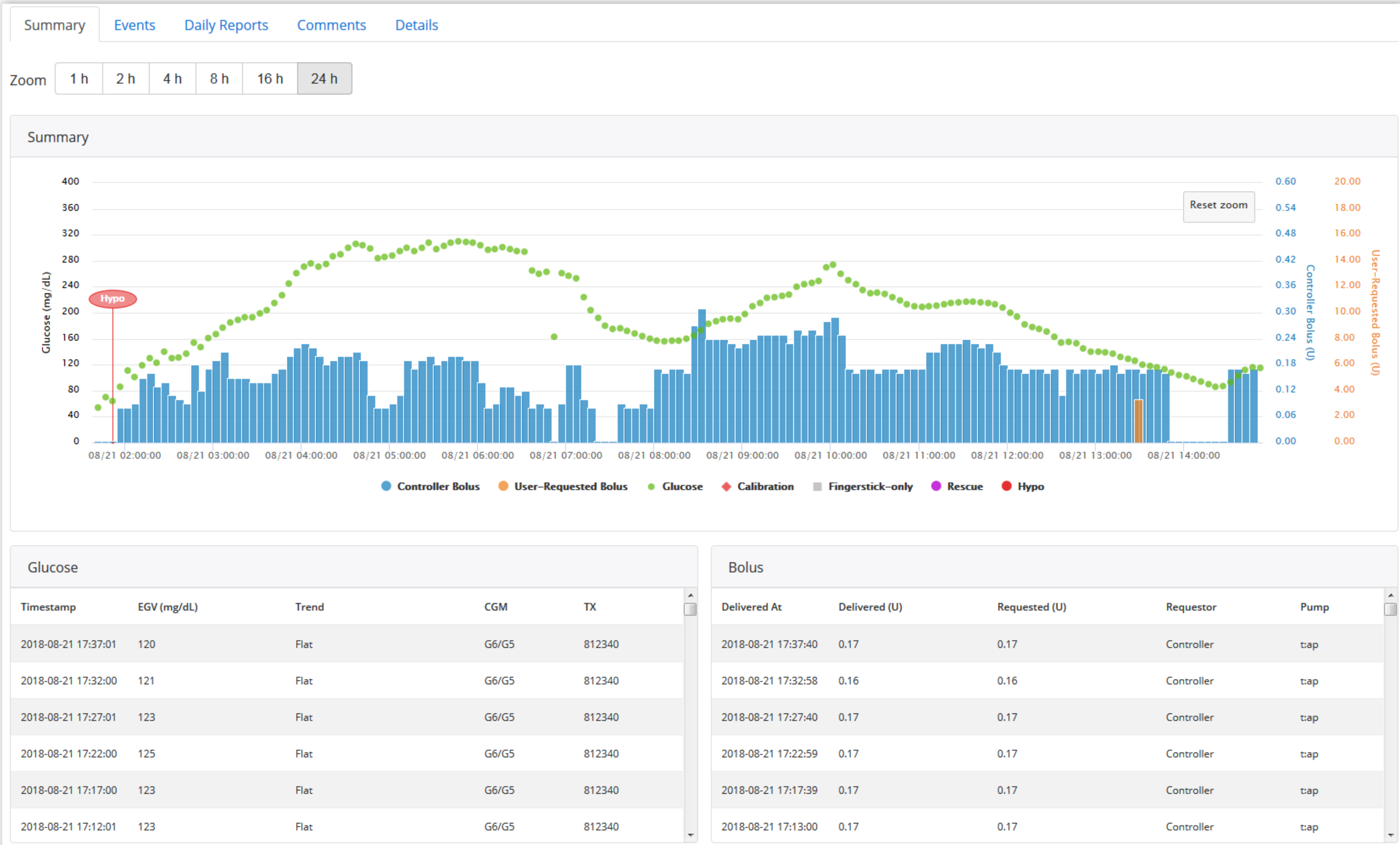
- Summary
- Events
- Daily Reports
- Comments
- Details

These are described in the rest of the appendix.

The summary sub-page contains graphical display of the following variables over last 24 hours as shown in Supplementary Figure 2:

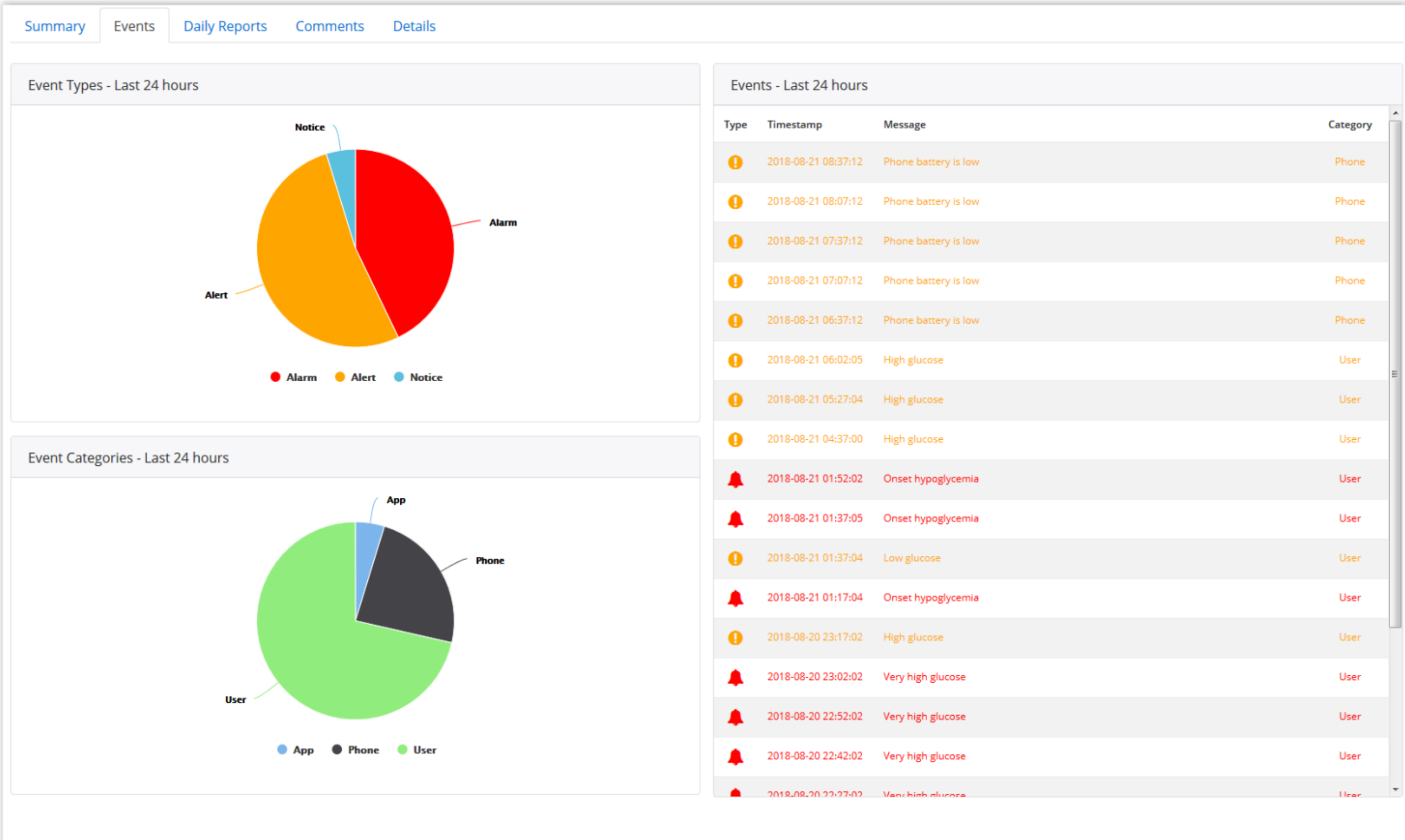
- Controller bolus
- User-requested bolus
- Glucose (CGM)
- Calibration
- Fingerstick glucose
- Hypoglycemia alarm flag
- Rescue carbs flag

The user can zoom in and out on the desired portion of the graphical display. A table of historical glucose and bolus information is also provided as shown in Supplementary Figure 2.



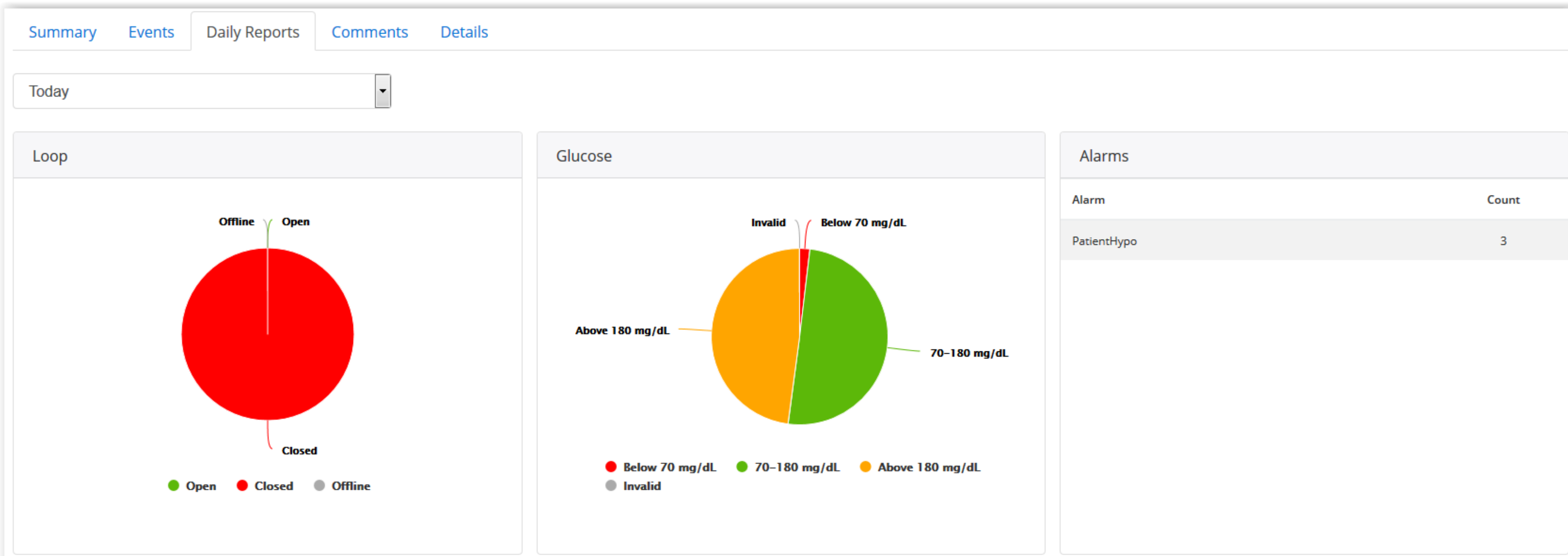
Supplementary Figure 2. Summary page of the RM portal.

The Events subpage shows the iAPS event information over the last 24 hours as shown in Supplementary Figure 3. The events are grouped by types as the previously described: notices, alerts and alarms, and by categories of sources: iAPS, CGM or the user.



Supplementary Figure 3. Events page of the RM portal.

The Daily Reports sub-page, as shown in Supplementary Figure 4, shows the day-by-day reports to allow the clinician perform a quick assessment of the glycemic control during the study and hence facilitates clinical decision making without waiting for data downloads from devices. The daily reports can be accessed for the last seven days where for each day information is provided for percent time in closed-loop, percent time in various glucose targets, and alarms generated during the study.



Supplementary Figure 4. Daily Reports page of the RM portal.

Finally, the Comments sub-page (not shown) allows access to clinician notes while the Details sub-page (not shown) summarizes the clinical parameters such as iAPS user id, information about site, study and protocol, glucose alert levels, and subject specific information such as basal rate, carb ratio, correction factor and total daily insulin values.

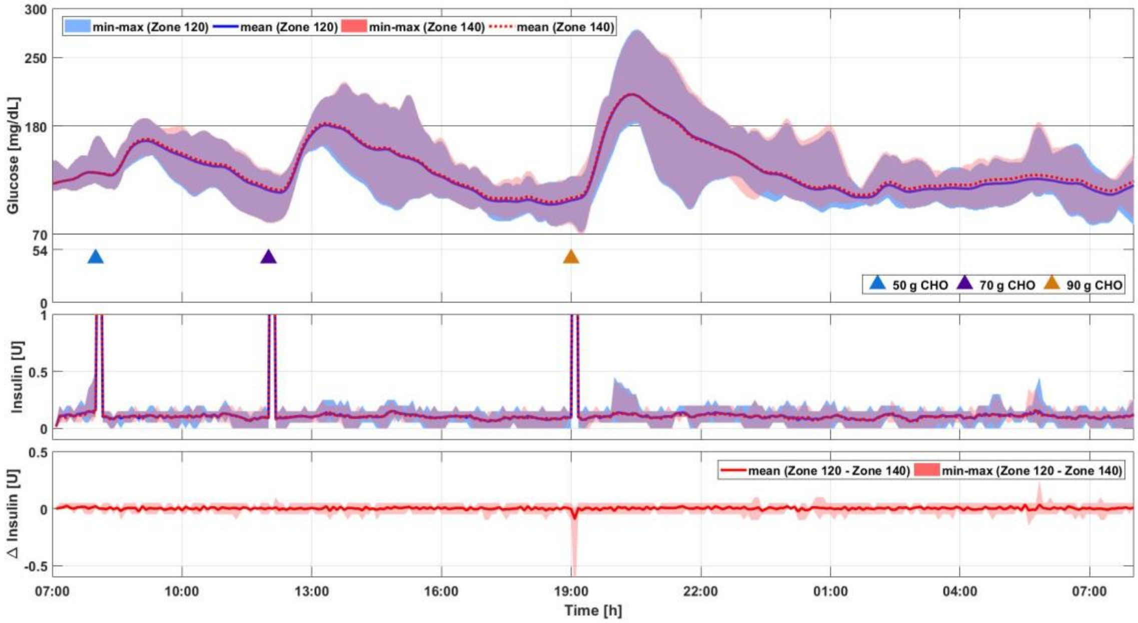
APPENDIX-III: Performance Evaluation Upon Changing Upper Zone in the Controller

To illustrate the effect of changing the upper zone in Zone MPC from 140 mg/dL to 120 mg/dL in order to improve glycemic performance, we simulated a 24h scenario with a meal plan consisting of 50g, 70g and 90g of carbohydrates. The glucose and insulin delivery profiles from 10 simulated participants for both upper zone values 140 mg/dL and 120 mg/dL are shown in Supplementary Figure 5. While the two controllers tuning performed in a similar manner, the mean glucose was statistically significantly reduced by ≈3 mg/dL throughout the day and by ≈2 mg/dL overnight, while the total insulin delivered was only marginally increased (Supplementary Table 2, Supplementary Figure 5).

Supplementary Table 2. Glycemic metrics comparing the zone MPC with upper zone = 120 mg/dL and upper zone=140 mg/dL under announced meals scenario and 10 repeat simulations. Data in this table are shown as mean (SD) and statistical significance is assessed by paired t-test.

	Day and night			**Overnight (24:00 – 06:00)**		
	Zone 120	Zone 140	p-value	Zone 120	Zone 140	p-value
% Time < 54 mg/dL	0 (0)	0 (0)	-	0 (0)	0 (0)	-
% Time < 70 mg/dL	0 (0)	0 (0.1)	0.343	0 (0)	0 (0)	-
% Time 70-180 mg/dL	89.8 (6.1)	89.3 (6.1)	0.139	99.9 (0.4)	99.3 (1.4)	0.17
% Time > 250 mg/dL	0.4 (1.4)	0.5 (1.5)	0.343	0 (0)	0 (0)	-
Mean glucose (mg/dL)	135.3 (7.3)	137.2 (7.8)	0.003	117.4 (5.9)	120.4 (7.1)	<0.001
Total insulin (U)	43.9 (9.3)	43.4 (9.2)	0.001	7.4 (1.8)	7.3 (1.7)	0.012
SD glucose (mg/dL)	30.9 (7.2)	30.2 (7.1)	0.07	13.5 (4.5)	13.9 (4.3)	0.428
Mean glucose at 0700 h (mg/dL)	118.8 (11.5)	120.5 (10.9)	0.032	-	-	-

Supplementary Figure 5. In-silico evaluation of 10 subjects under announced meals. The plots show glucose and insulin profiles and difference in insulin delivered between subjects for controller with upper zone = 120 mg/dL and upper zone = 140 mg/dL.



APPENDIX-IV: Real-Life Simulation Tests

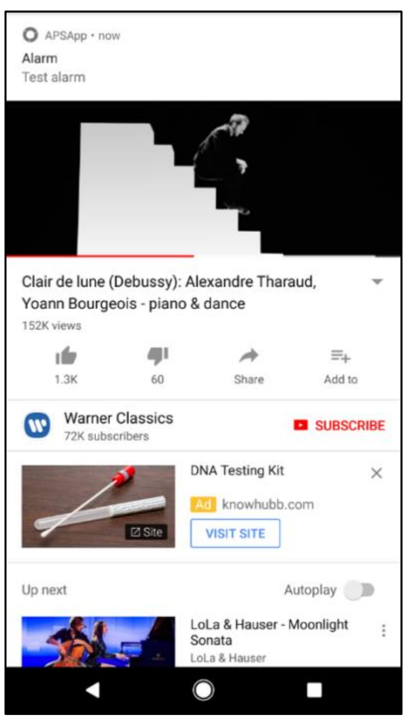
We performed tests to verify extended, continuous operation of iAPS running with third party apps and simulated real-life use in unconstrained environments. The test cases were designed to cover typical use cases such as streaming media (**Test Case 1**), playing games (**Test Case 2**), connecting to electronics devices (**Test Case 3**), regular use of smartphone (**Test Case 4 and 5**) and limited smartphone memory and processor resources (**Test Case 6**). The tests were performed for two system configurations:

1. **System A**: Dexcom G5 CGM, Tandem t:AP pump and iAPS on Google Pixel smartphone running Android 7.1
2. **System B**: Dexcom G5 CGM, Omnipod pump and iAPS on Google Pixel smartphone running Android 7.1

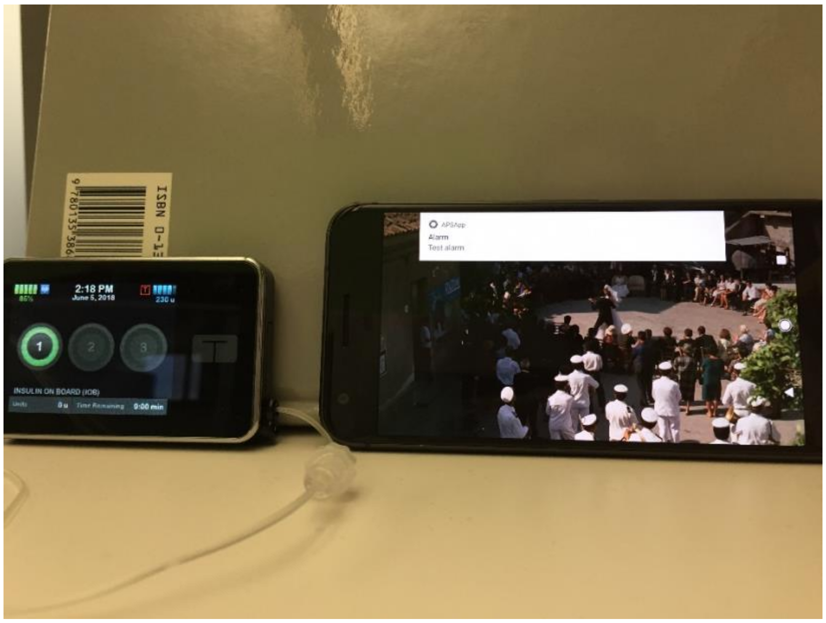
The test case procedures and outcomes are described below.

Test Case 1. Streaming media while system is in closed-loop

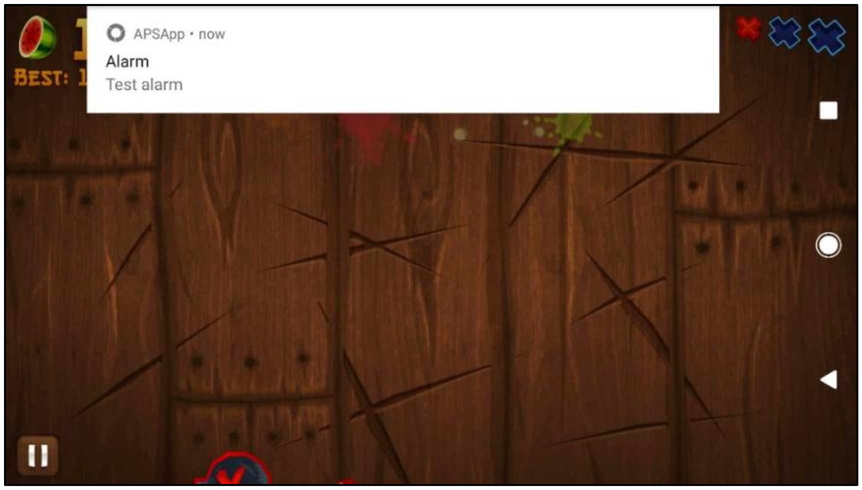
a. **Playing video on YouTube app while system is in closed-loop.** Using System B configuration in closed-loop, the tester started playing a video on the YouTube app in full screen. The tester observed the test-setup over 24 hours while interacting with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server. The iAPS notifications were generated while YouTube video was running in full screen as shown below.

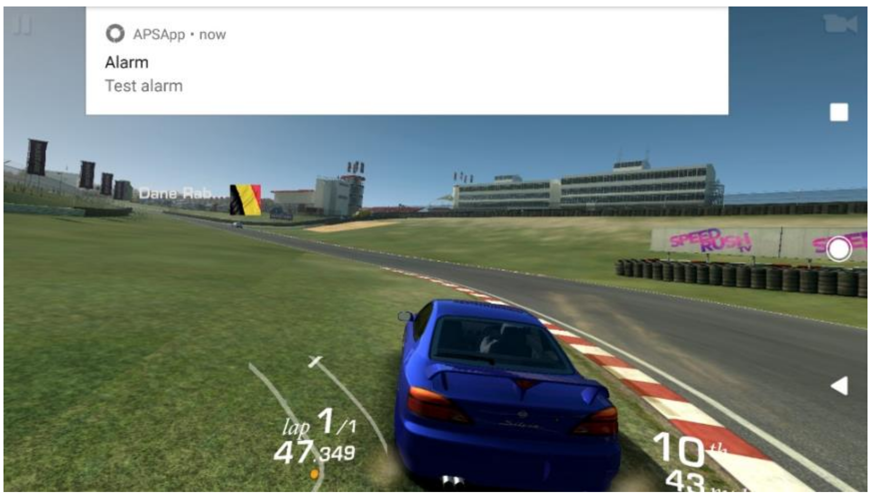


b. **Playing movie on Netflix app while system is in closed-loop.** Using System A configuration in closed-loop, the tester started playing a movie on the Netflix app in full screen. The tester observed the test-setup over 3 hours while interacting with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server. The iAPS notifications were generated while Netflix movie was running in full screen as shown below.

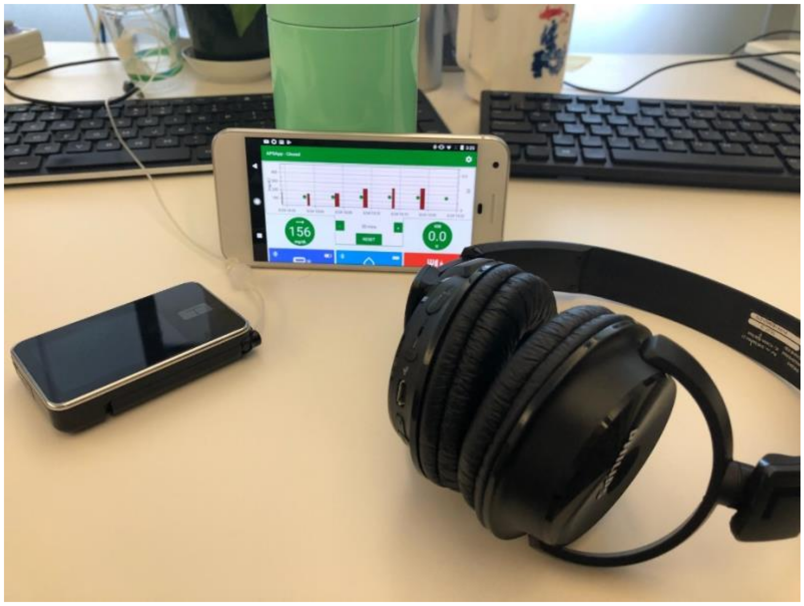


Test Case 2. Playing games while system is in closed-loop. Using System A configuration in closed-loop, the tester started playing games which were CPU and graphics intensive. The tester observed the test-setup over the next 1 hour while interacting with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server. The iAPS notifications were generated while the games were running in full screen as shown below.





Test Case 3. Wireless Bluetooth headphones use while system is in closed-loop. Using System A configuration in closed-loop, the tester paired to a wireless Bluetooth headphone. After verifying that sound is audible in the headphones by playing a YouTube video, the tester observed the test-setup (shown below) over <u>8 hours</u> (or till the headphone battery ran out) while interacting with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server.



Test Case 4. Using phone camera while system is in closed-loop. Using System B configuration in closed-loop, the tester used the smartphone camera app and started recording a video for 15 min while interacting with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server. The iAPS notifications were generated while the camera was active as shown below.

Test Case 5. Texting and calling while system is in closed-loop. Using both System A and System B configuration in closed-loop, the testers started using the cellular text messaging, multimedia messaging and cellular calls for 15 min while interacting with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server.

Test Case 6. Using smartphone memory and processor resources while system is in closed-loop

Using both System A and System B in closed-loop:

a. **Stress test.** The tester used Your Battery Drainer app for 3 hours. This app drains the phone battery by activating at once all the following battery intensive tasks such as: wake lock with full screen brightness, use of WiFi to continuously issue http requests, use of Bluetooth and continuous issuing of scan commands, and use of GPS and heavy CPU operations. During the 3-hour period, the tester interacted with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server. The iAPS notifications were generated while the system was running.

b. **Low random access memory test.** The tester used Fill RAM memory app for 3 hours. This app fills up the phone RAM memory to the user directed level. The tester requested filling RAM such that less than 500 MB was left. During the 3-hour period, the tester interacted with the iAPS as required (e.g., to request a meal bolus). The iAPS ran in the background and performed active insulin management without any interruptions for the test duration with data continuously logged in the remote server. The iAPS notifications were generated while the system was running.

In both tests, the iAPS performed without any error although it was limited by available RAM and CPU processing power.

APPENDIX-V: Individual Subject Data Tables

The following tables present glycemic metrics, using the complete CGM data, comparing the one-week sensor-augmented pump (SAP) run-in period to the 48-hour AP study for the six study subjects.

Subject 1

CGM Metric	SAP	Closed-loop
Mean glucose (mg/dL)	158.13	149.49
SD glucose (mg/dL)	57.13	39.62
% Time		
< 54 mg/dL	0.09	0.08
< 60 mg/dL	0.26	0.19
< 70 mg/dL	0.61	0.53
70-140 mg/dL	43.38	45.6
70-180 mg/dL	74.2	76.29
> 180 mg/dL	25.19	23.18
> 250 mg/dL	7.36	0.49
> 300 mg/dL	2.71	0

Subject 2

CGM Metric	SAP	Closed-loop
Mean glucose (mg/dL)	142.23	130.1
SD glucose (mg/dL)	44.62	32.88
% Time		
< 54 mg/dL	0.34	0
< 60 mg/dL	0.96	0
< 70 mg/dL	2.89	0.87
70-140 mg/dL	49.5	63.4
70-180 mg/dL	76.47	90.57
> 180 mg/dL	20.64	8.57
> 250 mg/dL	1.31	0
> 300 mg/dL	0	0

Subject 3

CGM Metric	SAP	Closed-loop
Mean glucose (mg/dL)	139.54	161.9
SD glucose (mg/dL)	49.15	52.26
% Time		
< 54 mg/dL	0.03	0
< 60 mg/dL	0.22	0
< 70 mg/dL	1.15	0
70-140 mg/dL	56.76	35.73
70-180 mg/dL	80.12	62.84
> 180 mg/dL	18.72	37.16
> 250 mg/dL	2.79	3.24
> 300 mg/dL	0.83	0

Subject 4

CGM Metric	SAP	Closed-loop
Mean glucose (mg/dL)	111.17	110.3
SD glucose (mg/dL)	53.15	28.03
% Time		
< 54 mg/dL	3.89	0
< 60 mg/dL	6.69	0
< 70 mg/dL	15.29	3.33
70-140 mg/dL	63.96	78.39
70-180 mg/dL	74.99	96.35
> 180 mg/dL	9.72	0.32
> 250 mg/dL	2.92	0
> 300 mg/dL	1.18	0

Subject 5

CGM Metric	SAP	Closed-loop
Mean glucose (mg/dL)	130.24	135.76
SD glucose (mg/dL)	44.66	39.95
% Time		
< 54 mg/dL	4.06	0.58
< 60 mg/dL	5.46	1.35
< 70 mg/dL	8.82	5.25
70-140 mg/dL	50.07	51.51
70-180 mg/dL	78.67	81.09
> 180 mg/dL	12.52	13.66
> 250 mg/dL	0.95	0
> 300 mg/dL	0	0

Subject 6

CGM Metric	SAP	Closed-loop
Mean glucose (mg/dL)	112.67	128.94
SD glucose (mg/dL)	34.77	32.39
% Time		
< 54 mg/dL	2.45	0
< 60 mg/dL	3.7	0.67
< 70 mg/dL	7.79	3.33
70-140 mg/dL	70.09	53.49
70-180 mg/dL	88.17	91.49
> 180 mg/dL	4.03	5.18
> 250 mg/dL	0	0
> 300 mg/dL	0	0