Supplementary Materials

Scoring System

This system was created to assess the optimal control range for the AI based controller presented in this article. However, it could also be used to compare the results of different closed loop glucose controllers through application of a uniform scoring method, assuming the different controllers attempted to control to the same range.

The scoring system was designed to give a scoring range of 0-30 points for time in range 70-140 mg/dl, as maximizing time in this range has been shown to correlate with decreasing mortality rates[36]. Time in range should be rounded down to the nearest whole number, and any time in range of less than 71% would receive a score of zero. The scores will otherwise progress from one for 71% time in range up to thirty for 100% time in range. Perfect scores of thirty are not to be expected. This progression is noted in the table below.

The scoring system was designed to give a scoring range of 0-30 points for coefficient of variation (CV), as minimizing the CV has been shown to correlate with decreasing mortality rates[35]. A score of zero is given for a CV of 34% or greater. A score of one is given for a score of 33% to less than 34%, with a progressive increase in score for each absolute one percentile lowering of the CV, until a top score of thirty for a CV less than 5%. Coefficients of variations are rounded to the nearest one-tenth percentile. Perfect scores of thirty are not to be expected. This progression is noted in the table below.

The scoring system was designed to give a scoring range of -40 to 30 points for hypoglycemia, as minimizing the time spent in the hypoglycemic range has been shown to correlate with decreasing mortality rates[43], and it is felt that any time spent in moderate to severe hypoglycemia (ex < 50 mg/dL) should be penalized. If any glucose values < 40 are recorded, a score of -10 is given. For the range of 40 to 49 each number is given a score of either 0 or -3. For each number, if no values are recorded a score of 0 is given, however if even one value is recorded for a given number a score of -3 is given. The maximum negative score allowed for each number is -3, and for the entire range it is -30. Thus, if there are only two values recorded in this range (ex 42 and 47) the controller receives a score of -6. If each value in range of 40-49 mg/dl is recorded by the controller the max score of -30 would be received. In order to determine the scores for the range of 50-69 mg/dl, the average percent of all hypoglycemic values for each number in this range was determined for the AI controller when it performed at its worst with regards to hypoglycemia in two separate tests. This occurred with a control range of 70-110 mg/dl, sensor error of 15% with both clinical (A-D, see below) and nonclinical (E, see below) dextrose infusions. When calculating these percentiles only the glucose values < 70 mg/dl were considered. For the 50 to 59 mg/dl range, if the controller being evaluated has a percentile score for each number less than or equal to the AI controller, then it would receive a score of 2. If the percentile score is greater than the AI controller then it would receive a score of 0. The same method is applied to the range of 60-69 mg/dl, however the two potential scores are 1 and 0. There are no positive scores given for avoiding glucose values < 50 mg/dl as it is felt controllers should not be rewarded a positive score for achieving a result that should be

fundamental to every well designed closed loop glucose controller. The overall schema of the hypoglycemic scoring system is to penalize for significant hypoglycemia (ex < 50 mg/dl), and reward for achieving low percentiles in the range of 50-69 mg/dl. The range of 50-59 mg/dl is more heavily weighted than the range of 60-69 mg/dl, as avoiding the lower range of hypoglycemia (50-59 mg/dl) is more important than avoiding the upper range of hypoglycemia (60-69 mg/dl).

The scoring system was designed to give a scoring range of 0-10 points for the percent of values in the hyperglycemic range of greater than 140 mg/dl, as minimizing the degree of hyperglycemia has been shown to correlate with decreasing mortality rates[47]. The hyperglycemic score was less heavily weighted than the other three as it is the author's opinion (LD) poor performance in this glucose metric has a less significant effect on increasing mortality rates.

The minimum total score possible is -40, while the maximum score possible is 100. No controller should be expected to achieve a score of 100.

A) Scoring system components

1. Time in Range Scoring System

Percent all glucose values in range of 70-140 mg/dl	Score
100%	30
99%	29
98%	28
97%	27
96%	26
95%	25
94%	24
93%	23
92%	22
91%	21
90%	20
89%	19
88%	18
87%	17
86%	16
85%	15
84%	14
83%	13
82%	12
81%	11
80%	10
79%	9
78%	8
77%	7
76%	6
75%	5
74%	4
73%	3
72%	2
71%	1
<71%	0

2. Coefficient of Variation Scoring System

Coefficient of Variation (Standard deviation/mean glucose)	Score
<5%	30
5 to <6%	29
6 to <7%	28
7 to < 8%	27
8 to <9%	26
9 to <10%	25
10 to <11%	24
11 to <12%	23
12 to <13%	22
13 to < 14%	21
14 to < 15%	20
15 to <16%	19
16 to < 17%	18
17 to < 18%	17
18 to <19%	16
19 to < 20%	15
20 to < 21%	14
21 to < 22%	13
22 to < 23%	12
23 to < 24%	11
24 to < 25%	10
25 to < 26%	9
26 to < 27%	8
27 to < 28%	7
28 to < 29%	6
29 to <30%	5
30 to < 31%	4
31 to < 32%	3
32 to < 33%	2
33 to < 34%	1
>= 34%	0

3. Hypoglycemic Scoring System

Glucose value in hypoglycemic range (mg/dl)	Allowed Percentile (AP) = (# values/ total # values < 70) * 100	Score (<= AP/> AP)
<40	0	0/-10
40	0	0/-3
41	0	0/-3
42	0	0/-3
43	0	0/-3
44	0	0/-3
45	0	0/-3
46	0	0/-3
47	0	0/-3
48	0	0/-3
49	0	0/-3
50	0.03	2/0
51	0.08	2/0
52	0.14	2/0
53	0.19	2/0
54	0.30	2/0
55	0.33	2/0
56	0.50	2/0
57	0.62	2/0
58	0.92	2/0
59	1.22	2/0
60	1.64	1/0
61	2.13	1/0
62	2.75	1/0
63	3.50	1/0
64	4.95	1/0
65	6.48	1/0
66	9.10	1/0
67	12.38	1/0
68	23.47	1/0
69	29.24	1/0

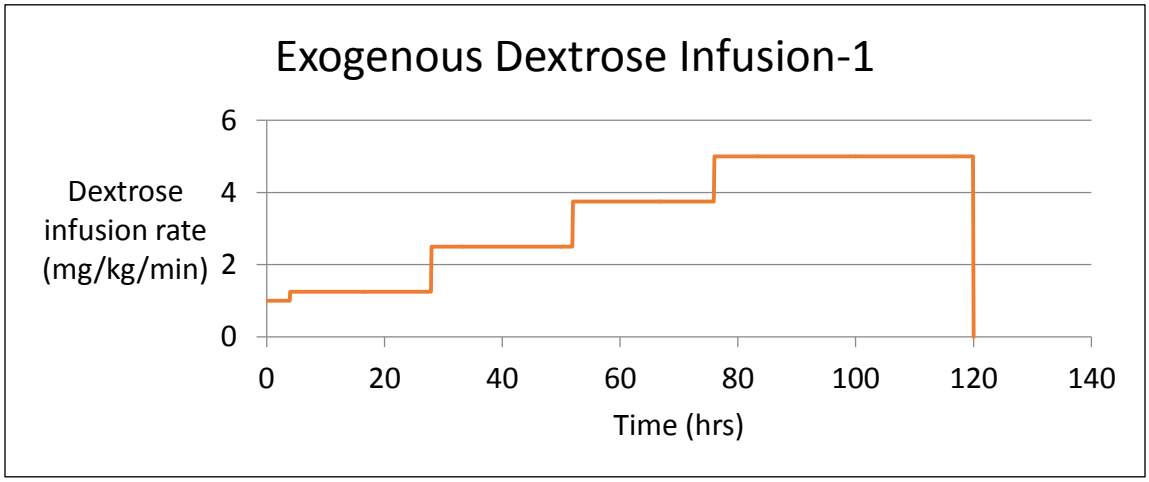
4. Hyperglycemic Scoring System

Percent all glucose values > 140 mg/dl	Score
0 to < 1%	10
1 to < 2%	9
2 to < 3%	8
3 to < 4%	7
4 to < 5%	6
5 to < 6%	5
6 to < 7%	4
7 to < 8%	3
8 to < 9%	2
9 to < 10%	1
>= 10%	0

B) Dextrose infusion tables used to perturb system (F_{EG})

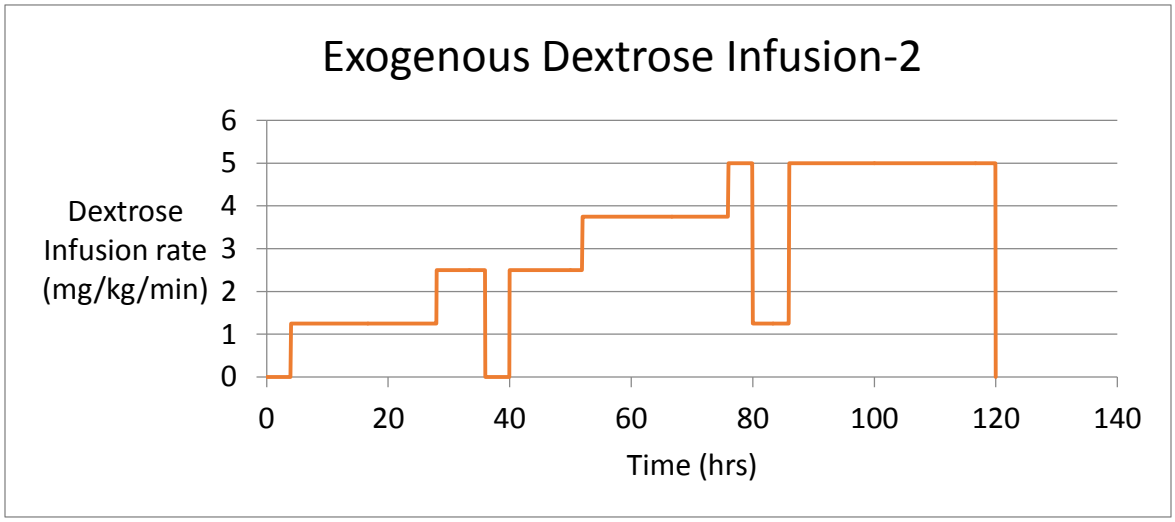
1) Gradual escalation of IV dextrose

Dextrose infusion (mg/kg/min)	From time (hr)	To time (hr)
1	0	4
1.25	4	28
2.5	28	52
3.75	52	76
5	76	120



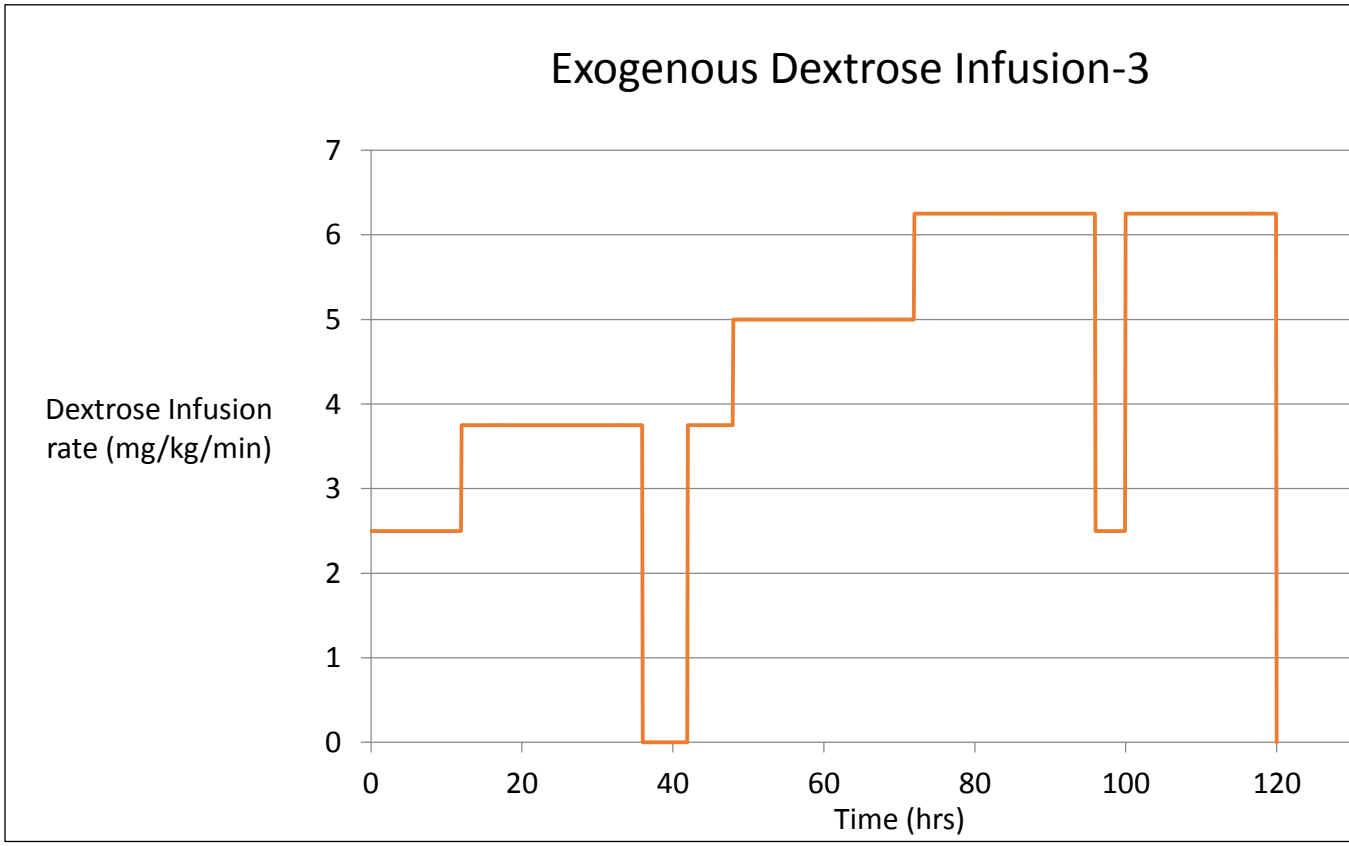
2) Patient taken to OR at times 36 & 80 hours, changed to normal saline with first trip to OR and D5 with second trip

Dextrose infusion (mg/kg/min)	From time (hr)	To time (hr)
0	0	4
1.25	4	28
2.5	28	36
0	36	40
2.5	40	52
3.75	52	76
5	76	80
1.25	80	86
5	86	120



3) Patient taken to OR at time 36 hours and changed to normal saline, taken to OR at time 96 and changed to D10, otherwise aggressive escalation of dextrose support

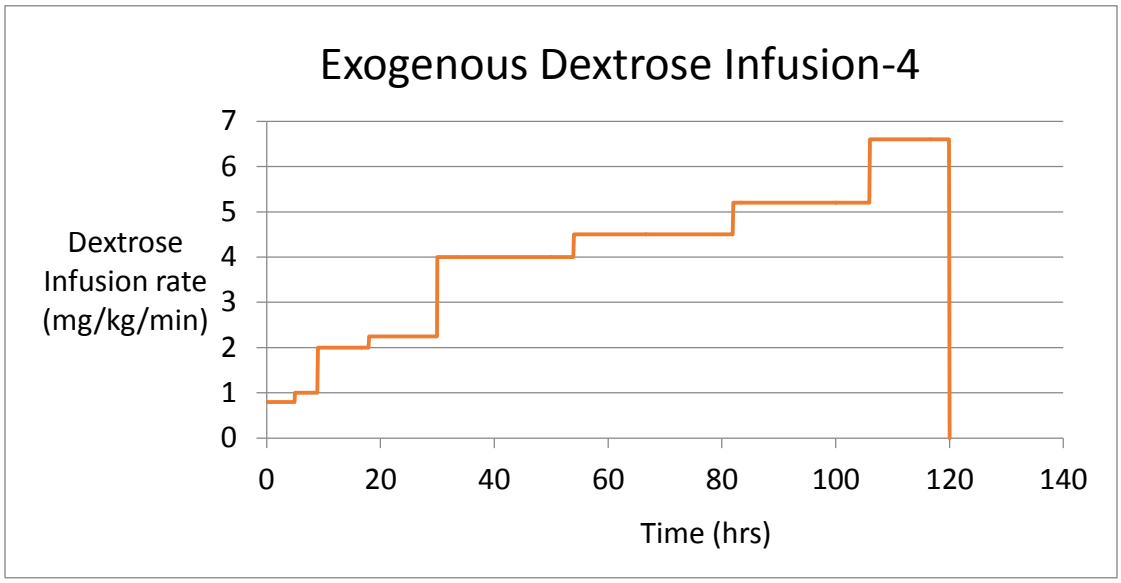
Dextrose infusion (mg/kg/min)	From time (hr)	To time (hr)
2.5	0	12
3.75	12	36
0	36	42
3.75	42	48
5	48	72
6.25	72	96
2.5	96	100
6.25	100	120



4) Slow and gradual escalation of dextrose support

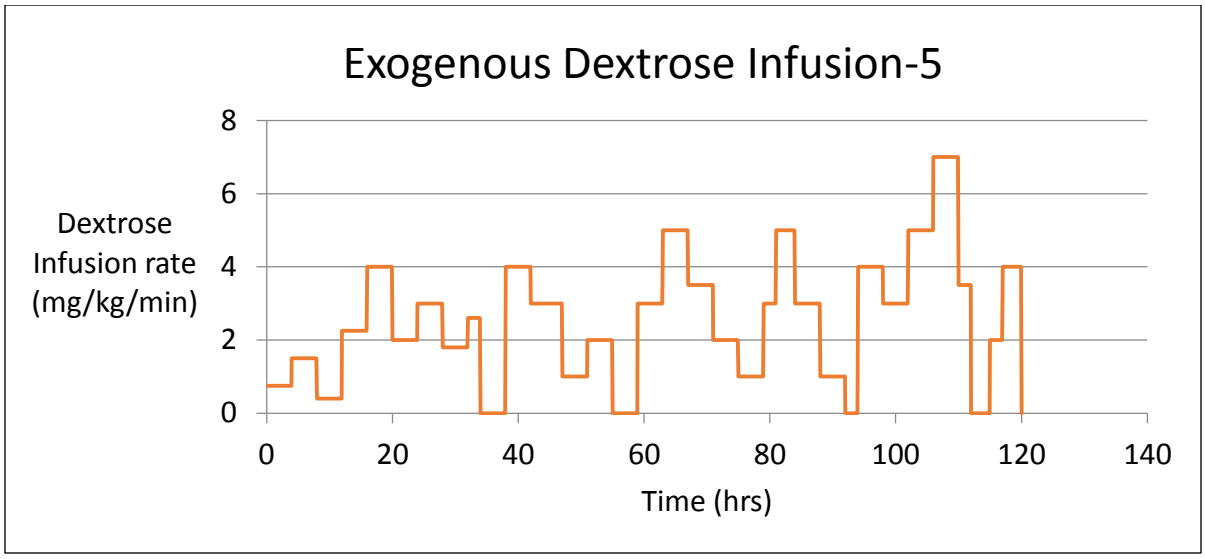
Dextrose infusion (mg/kg/min)	From time (hr)	To time (hr)
0.8	0	5
1	5	9
2	9	18
2.25	18	30
4	30	54
4.5	54	82
5.2	82	106

6.6	106	120


Exogenous Dextrose Infusion-4
Dextrose Infusion rate (mg/kg/min)
7
6
5
4
3
2
1
0
0
20
40
60
80
100
120
140
Time (hrs)

5) Nonclinical dextrose infusion, used as “stress test” of controller

Dextrose infusion (mg/kg/min)	From time (hr)	To time (hr)
0.75	0	4
1.5	4	8
0.4	8	12
2.25	12	16
4	16	20
2	20	24
3	24	28
1.8	28	32
2.6	32	34
0	34	38
4	38	42
3	42	47
1	47	51
2	51	55
0	55	59
3	59	63
5	63	67
3.5	67	71
2	71	75
1	75	79
3	79	81
5	81	84
3	84	88
1	88	92
0	92	94
4	94	98
3	98	102
5	102	106
7	106	110
3.5	110	112
0	112	115
2	115	117
4	117	120

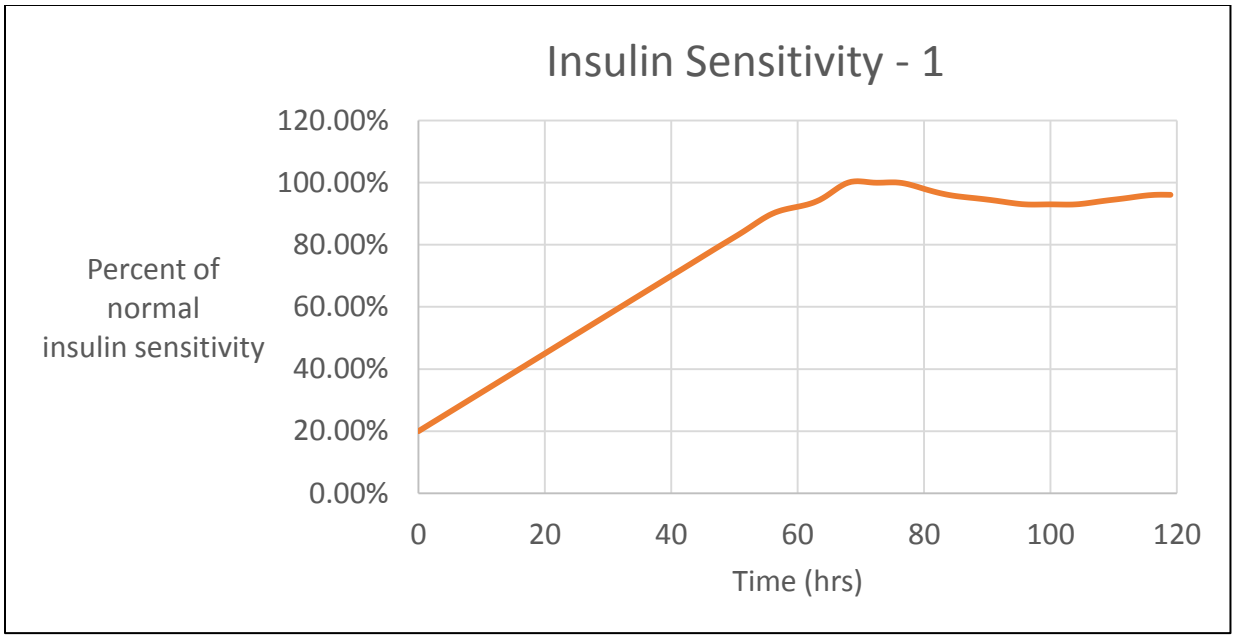

Exogenous Dextrose Infusion-5
Dextrose Infusion rate (mg/kg/min)
8
6
4
2
0
0
20
40
60
80
100
120
140
Time (hrs)

C) Time Variant Parameters – Tables used to create smooth curves via cubic spline interpolation technique

1. Time variant Insulin Sensitivity Curves

a) Insulin sensitivity curve 1 – Patient with extreme stress on admission, with medical and/or surgical therapy has improvement towards baseline sensitivity parameter of Van Herpe model

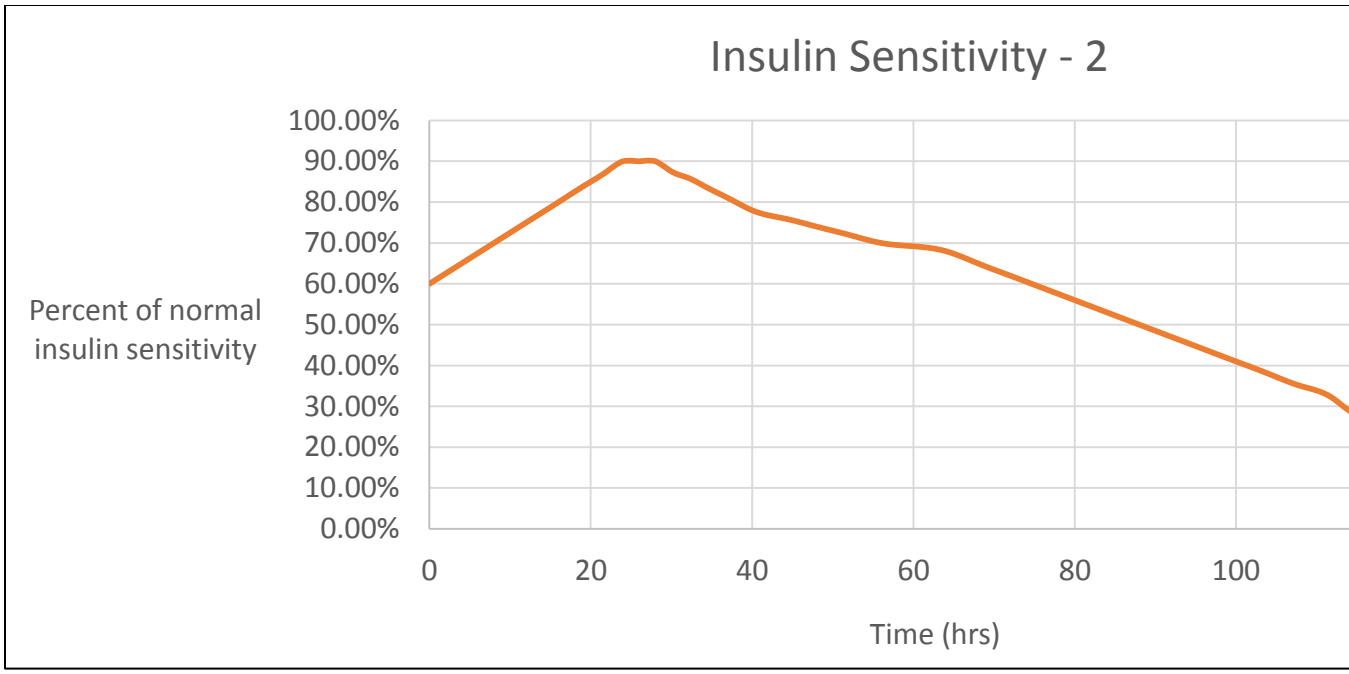
Time (Hr)	Insulin sensitivity multiplier ($i_s(t)$)
0	0.2
4	0.25
8	0.3
12	0.35
16	0.4
20	0.45
24	0.5
28	0.55
32	0.6
36	0.65
40	0.7
44	0.75
48	0.8
52	0.85
56	0.9
64	0.95
68	1
72	1
76	1
80	0.98
84	0.96
88	0.95
92	0.94
96	0.93
100	0.93
104	0.93
108	0.94
112	0.95
116	0.96
120	0.96


Insulin Sensitivity - 1
Percent of normal insulin sensitivity
120.00%
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
0
20
40
60
80
100
120
Time (hrs)

b) Insulin sensitivity curve 2 – Patient with moderate stress on admission secondary to trauma, however has escalation of stress induced insulin resistance secondary to sepsis from bowel perforation that was unrecognized on admission

Time (Hr)	Insulin sensitivity multiplier ($i_s(t)$)
0	0.6
4	0.65
8	0.7
12	0.75
16	0.8
20	0.85
22	0.875
24	0.9
26	0.9
28	0.9
30	0.875
32	0.86
34	0.84
36	0.82
38	0.8
40	0.78
44	0.76
48	0.74
52	0.72
56	0.7
64	0.68
68	0.65
72	0.62
76	0.59
80	0.56
84	0.53
88	0.5
92	0.47
96	0.44
100	0.41
104	0.38
108	0.35
112	0.32
114	0.29
116	0.27
118	0.25

120	0.23

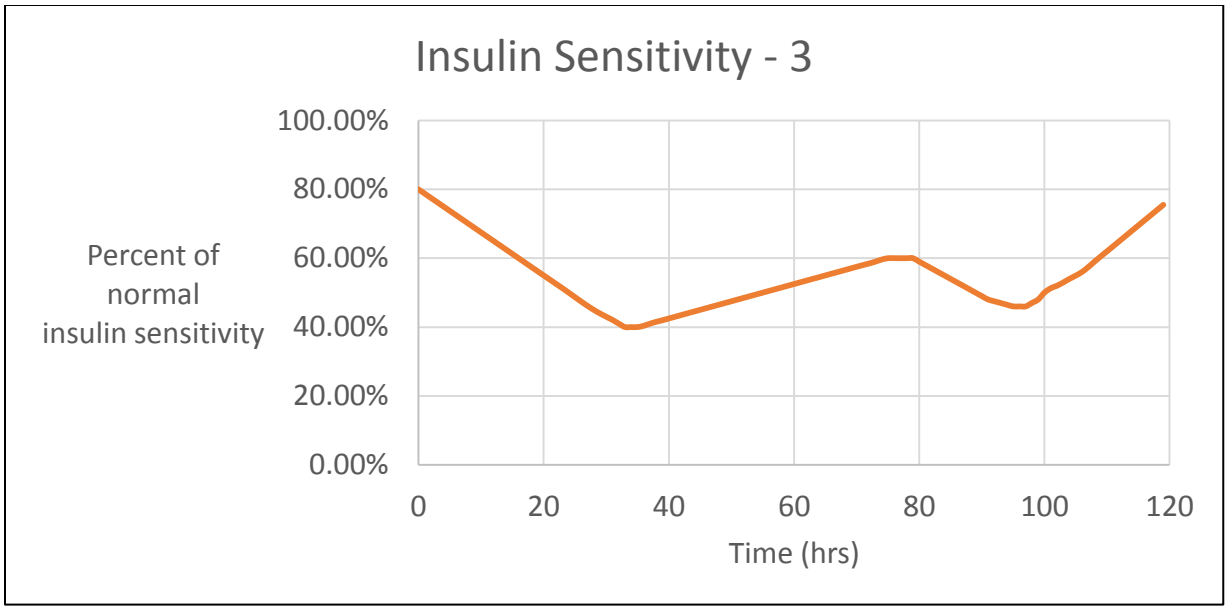


c) Insulin sensitivity curve 3 – Elective vascular surgery patient who develops multiple organ failure post op due to excessive blood loss during surgery

Time (Hr)	Insulin sensitivity multiplier ($i_s(t)$)
0	0.8
4	0.75
8	0.7
12	0.65
16	0.6
20	0.55
24	0.5
28	0.45
30	0.43
32	0.41
33	0.4
34	0.4
35	0.4
37	0.41
39	0.42
41	0.43
43	0.44
45	0.45
47	0.46
49	0.47

51	0.48
53	0.49
55	0.5
57	0.51
59	0.52
61	0.53
63	0.54
65	0.55
67	0.56
69	0.57
71	0.58
73	0.59
75	0.6
76	0.6
77	0.6
78	0.6
79	0.6
80	0.59
81	0.58
82	0.57
83	0.56
84	0.55
85	0.54
86	0.53
87	0.52
88	0.51
89	0.5
90	0.49
91	0.48
92	0.475
93	0.47
94	0.465
95	0.46
96	0.46
97	0.46
98	0.47
99	0.48
100	0.5
102	0.52
104	0.54
106	0.56
108	0.59
110	0.62

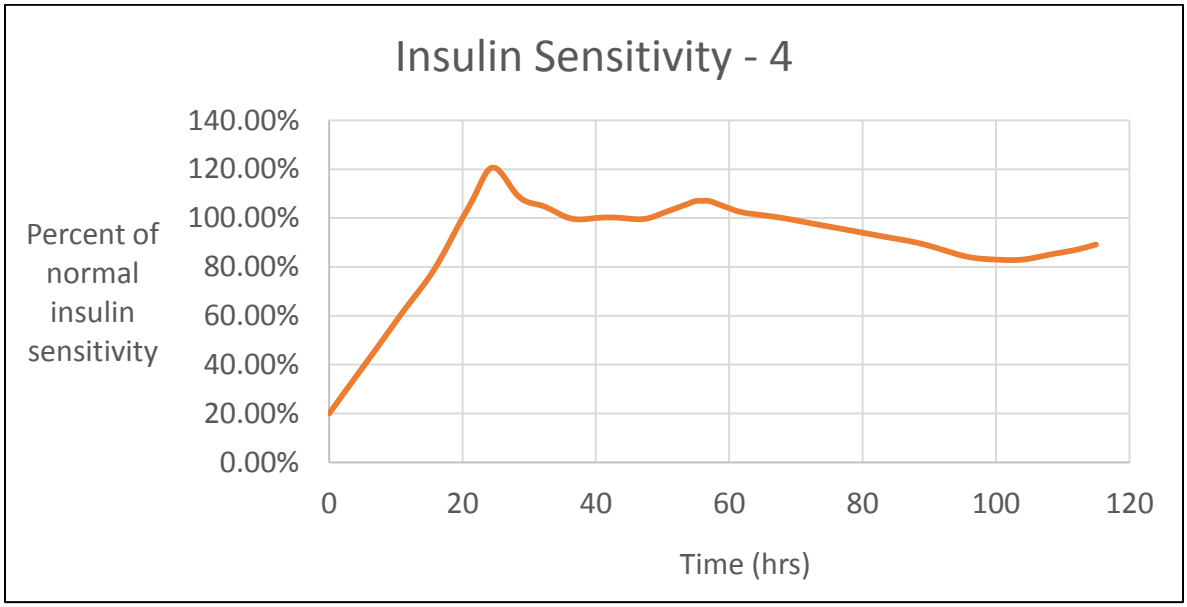
112	0.65
114	0.68
116	0.71
118	0.74
120	0.77



d) Insulin sensitivity curve 4 – Sepsis patient who has rapid improvement with volume/inotropic support causing severe insulin resistance to normalize within 24 hours.

Time (Hr)	Insulin sensitivity multiplier ($i_s(t)$)
0	0.2
4	0.35
8	0.5
12	0.65
16	0.8
20	1
22	1.1
24	1.2
28	1.1
32	1.05
36	1
40	1
44	1
48	1
50	1.02
51	1.03
52	1.04
53	1.05
54	1.06
55	1.07
56	1.07

57	1.07
58	1.06
59	1.05
60	1.04
61	1.03
64	1.015
68	1
72	0.98
76	0.96
80	0.94
84	0.92
88	0.9
92	0.87
96	0.84
100	0.83
104	0.83
108	0.85
112	0.87
116	0.9
120	0.9

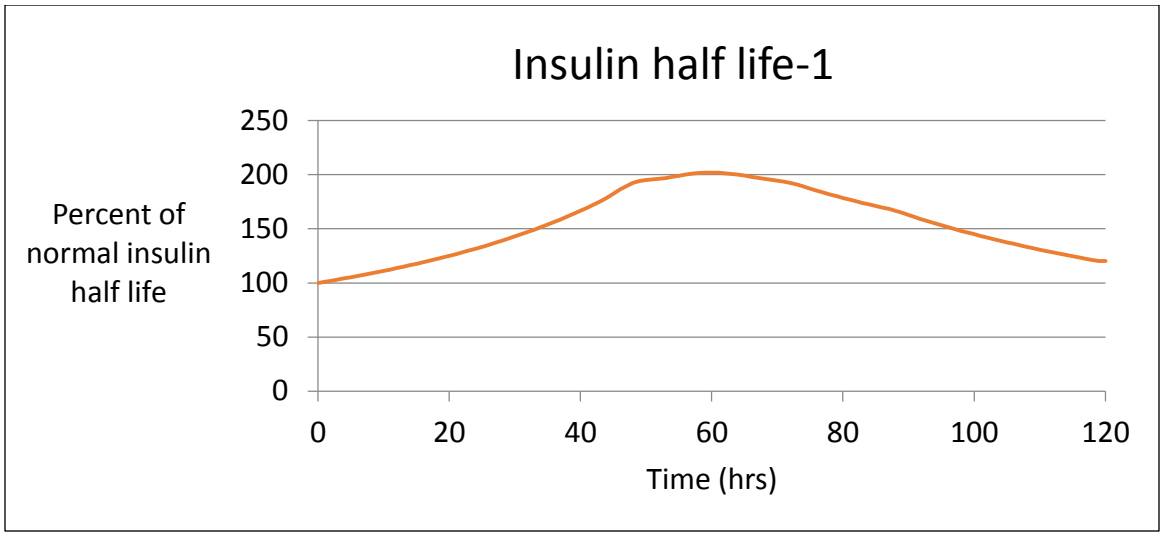


2. Time variant insulin Half-Life Curves

a) Insulin half-life curve 1 – Patient with normal renal function on admission, develops Acute Kidney Injury (AKI) due to presenting illness that is improving by 120 hours

Time (Hr)	Insulin half-life multiplier $i_h(t)$

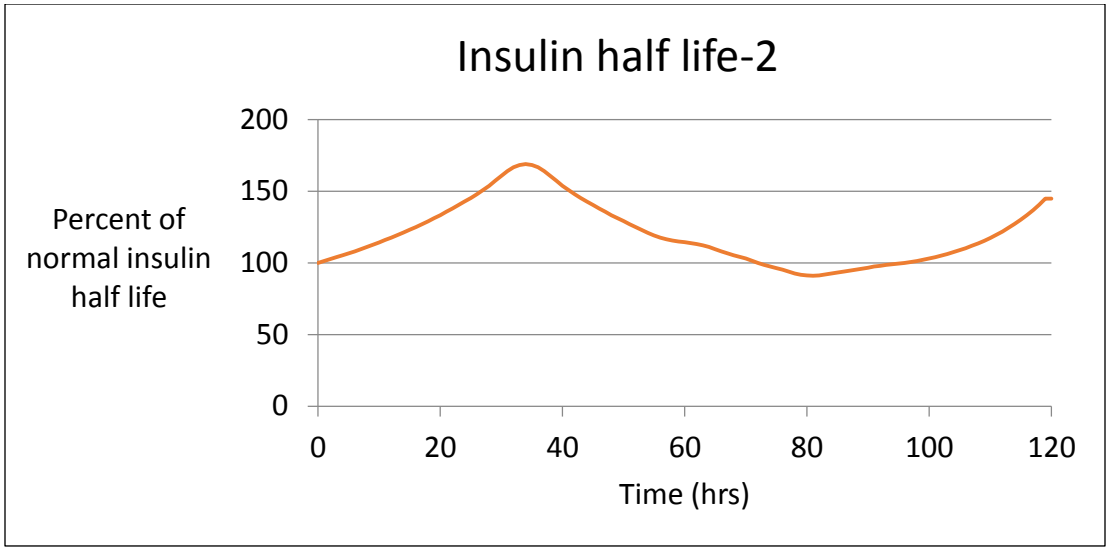
0	1
4	0.96
8	0.92
12	0.88
16	0.84
20	0.8
24	0.76
28	0.72
32	0.68
36	0.64
40	0.6
44	0.56
48	0.52
52	0.51
56	0.5
64	0.5
68	0.51
72	0.52
76	0.54
80	0.56
84	0.58
88	0.6
92	0.63
96	0.66
100	0.69
104	0.72
108	0.75
112	0.78
116	0.81
120	0.84



b) Insulin half-life curve 2 – Normal renal function on admission, patient develops mild AKI due to illness, improves by 72 hours but then again deteriorates as sepsis sets in

Time (Hr)	Insulin half-life multiplier $i_h(t)$
0	1
4	0.95
8	0.9
12	0.85
16	0.8
20	0.75
24	0.7
28	0.65
32	0.6
36	0.6
40	0.65
44	0.7
48	0.75
52	0.8
56	0.85
64	0.9
68	0.95
70	0.97
72	1
74	1.025
76	1.05
78	1.08
80	1.095
82	1.095

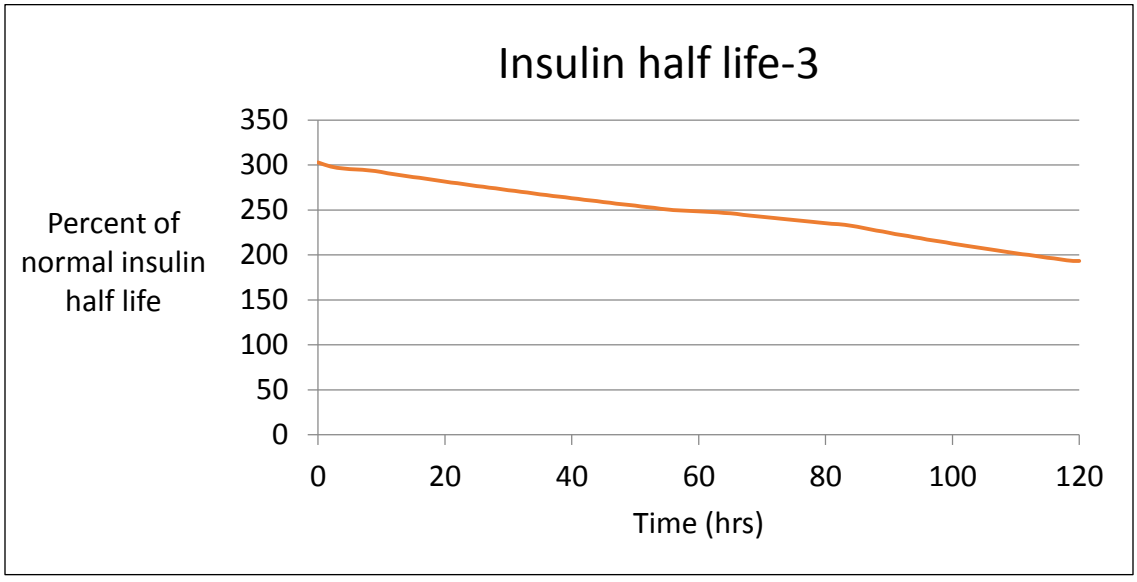
84	1.08
86	1.065
88	1.05
92	1.02
96	1
100	0.97
104	0.93
108	0.88
112	0.82
116	0.75
120	0.67



c) Insulin half-life curve 3 - Patient with chronic renal failure that improves somewhat during course of hospitalization with improved hydration status

Time (Hr)	Insulin half-life multiplier $i_h(t)$
0	0.33
2	0.335
8	0.34
12	0.345
16	0.35
20	0.355
24	0.36
28	0.365
32	0.37
36	0.375
40	0.38

44	0.385
48	0.39
52	0.395
56	0.4
64	0.405
68	0.41
72	0.415
76	0.42
80	0.425
84	0.43
88	0.44
92	0.45
96	0.46
100	0.47
104	0.48
108	0.49
112	0.5
116	0.51
120	0.52

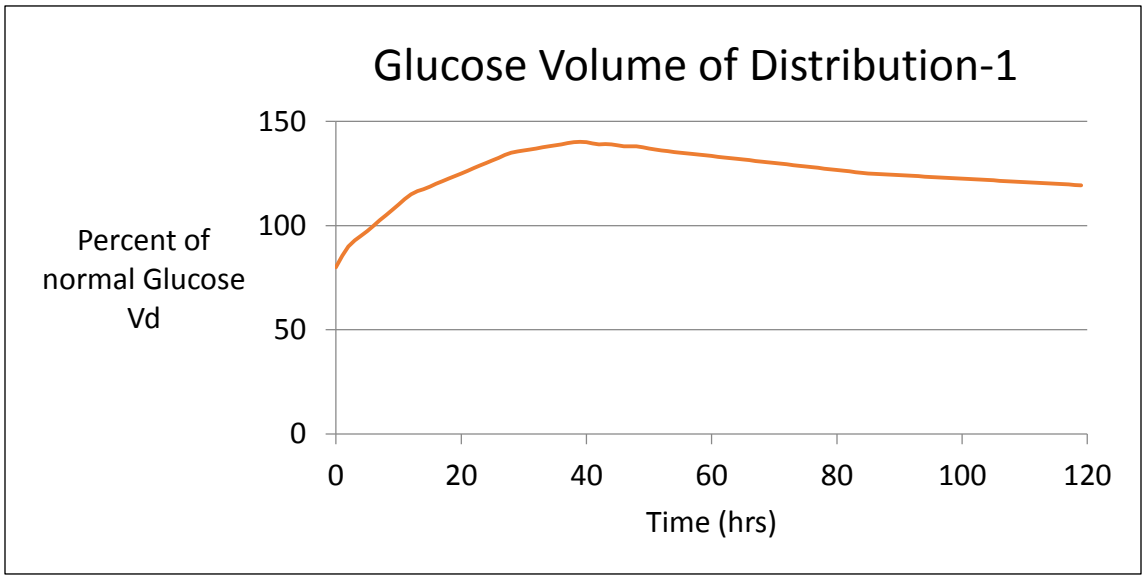


3. Time Variant Volume of Distribution Curves

a) Volume of distribution curve 1 – Trauma patient who is volume depleted on presentation, with resuscitation develops volume overload which is a natural course for trauma patients with capillary leak syndrome. Gradually returns towards baseline with diuresis.

Time (Hr)	Volume of distribution multiplier $V(t)$
0	0.8
2	0.9
4	0.95
6	1
8	1.05
10	1.1
12	1.15
14	1.175
16	1.2
18	1.225
20	1.25
22	1.275
24	1.3
26	1.325
28	1.35
30	1.36
32	1.37
34	1.38
36	1.39
38	1.4
40	1.4
42	1.39
44	1.39
46	1.38
48	1.38
50	1.37
52	1.36
55	1.35
58	1.34
61	1.33
64	1.32
67	1.31
70	1.3
73	1.29
76	1.28
79	1.27

82	1.26
85	1.25
88	1.245
91	1.24
94	1.235
97	1.23
100	1.225
103	1.22
106	1.215
109	1.21
112	1.205
115	1.2
118	1.195
120	1.19

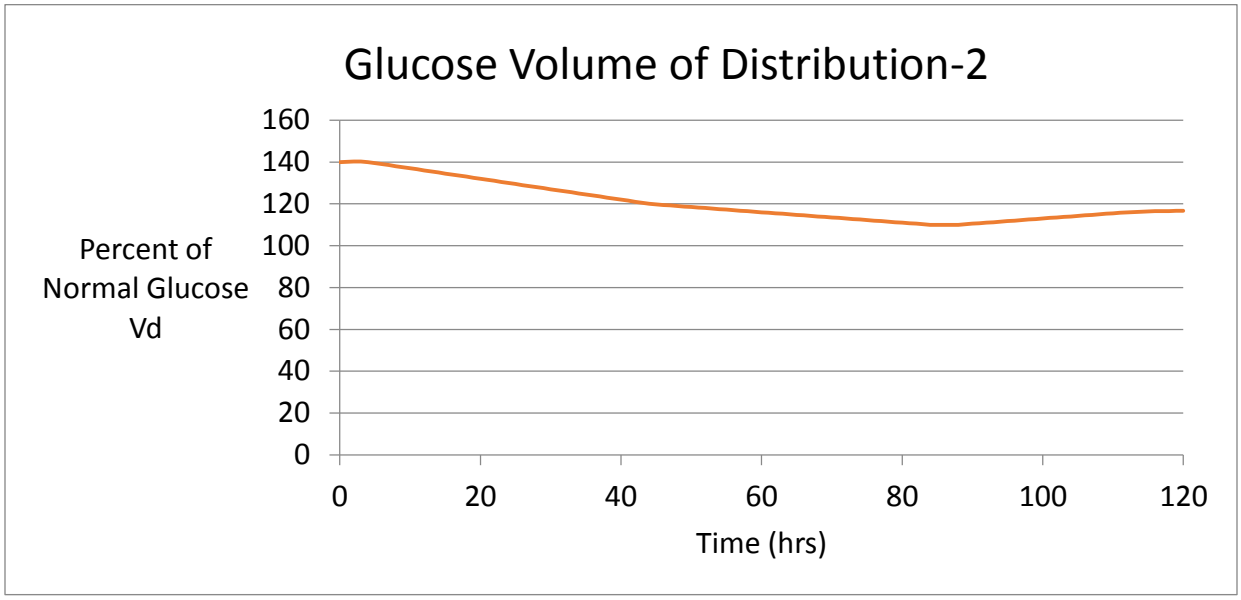


b) Volume of distribution curve 2 – Patient with congestive heart failure who is volume overloaded on presentation, but with diuresis volume overload status improves but never returns to baseline due to ongoing congestive heart failure

Time (Hr)	Volume of distribution multiplier $V(t)$
0	1.4
4	1.4
6	1.39
8	1.38
10	1.37
12	1.36
14	1.35

16	1.34
18	1.33
20	1.32
22	1.31
24	1.3
26	1.29
28	1.28
30	1.27
32	1.26
34	1.25
36	1.24
38	1.23
40	1.22
42	1.21
44	1.2
46	1.195
48	1.19
50	1.185
52	1.18
54	1.175
56	1.17
58	1.165
60	1.16
62	1.155
64	1.15
66	1.145
68	1.14
70	1.135
72	1.13
74	1.125
76	1.12
78	1.115
80	1.11
82	1.105
84	1.1
86	1.1
88	1.1
90	1.105
92	1.11
94	1.115
96	1.12
98	1.125
100	1.13

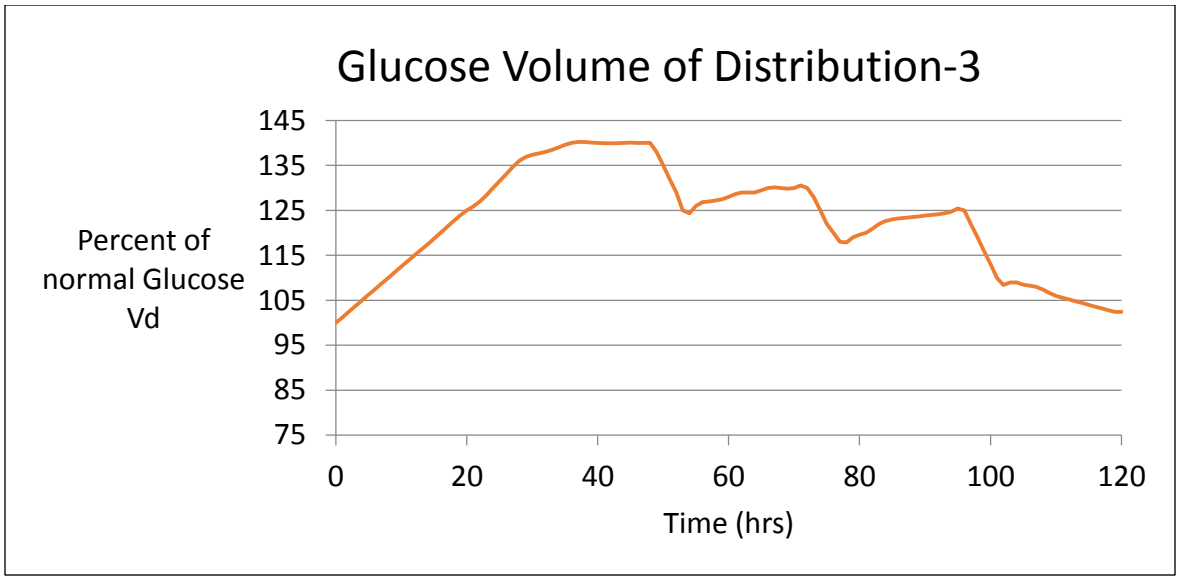
102	1.135
104	1.14
106	1.145
108	1.15
110	1.155
112	1.16
114	1.1625
116	1.165
118	1.1655
120	1.17



c) Volume of distribution curve 3 – Patient admitted for elective surgery, has excessive blood loss during surgery, develops capillary leak syndrome and Acute Kidney Injury. Undergoes daily dialysis for several days.

Time (Hr)	Volume of distribution multiplier $V(t)$
0	1
4	1.05
8	1.1
12	1.15
16	1.2
20	1.25
22	1.27
24	1.3
26	1.33
28	1.36
32	1.38
36	1.4
40	1.4
44	1.4
46	1.4
47	1.4
48	1.4
48.5	1.39
49	1.38
49.5	1.37
50	1.35
50.5	1.335
51	1.32
51.5	1.305
52	1.29
52.5	1.27
53	1.25
55	1.26
57	1.27
60	1.28
62	1.29
64	1.29
66	1.3
68	1.3
70	1.3
72	1.3
72.5	1.29
73	1.28

73.5	1.265
74	1.25
74.5	1.235
75	1.22
75.5	1.21
76	1.2
76.5	1.19
77	1.18
79	1.19
81	1.2
83	1.22
85	1.23
88	1.235
91	1.24
93.5	1.245
94.5	1.25
96	1.25
96.5	1.235
97	1.22
97.5	1.205
98	1.19
98.5	1.175
99	1.16
99.5	1.145
100	1.13
100.5	1.12
101	1.1
103	1.09
105	1.085
107	1.08
108.5	1.07
110	1.06
112.5	1.05
115	1.04
117.5	1.03
120	1.02



Note: While the above curves are all very real situations that happen on a daily basis during routine patient care, they should not be taken as the only possible scenarios. There are many possible patient scenarios that could be given to explain any combination of the above curves (insulin sensitivity, insulin half-life and volume of distribution) at any one point in time, especially since the curve parameters were kept within the bounds of what is seen clinically.

D) Comparative study as noted in Table 2

Overall set up – As noted in table, for each simulation the control range used is 80-120 mg/dl. This range was chosen as the AI controller tends to control towards the midpoint of the selected range, which in this range would be around 100 mg/dl. This is also the G_b of the Van Herpe model, thus can be looked at as the "set point" of the model that will be achieved if no exogenous dextrose/insulin is utilized. Starting glucose is 200 mg/dl as at this glucose level most institutions would consider instituting glucose control. A sensor error of 10% is chosen, as commercially available sensors are able to achieve this level of error. A bias of 0 is chosen, so as to not skew results based on an artefactual raising or lowering of treated glucose level. With 4 different glucose infusions to perturb the system and 80 in silico "patients" tested, each controller underwent 320 total simulations that lasted 5 days per simulation.

1. No control – simulated to highlight what would happen if the clinician elected to ignore the glucose level of the patients.

2. Represents results achieved by the AI controller developed by the authors and whose results are the main focus of the article. This controller has a base cycle of every 10 minutes, however will change to a cycle interval of every 5 minutes during states of hypoglycemia or when the glucose levels are rapidly changing.