Settings for your insulin (DIA and time-to-peak)

Contribution to the discussion among DIY loopers

The author assumes no liability   B/ V.2.5   May'24

Before doing any other tuning, make sure you are on the insulin you really want to be on, and have reasonably set the insulin-related parameters for your looping system.

In case you are just starting to loop and need to "household" with your time, all you need from this paper should be just two messages:

- Select your insulin in AAPS configuration, and refer to the data given in section 1.2.2 regarding DIA. To set it on 7 h is a fair guess for a start, if you are uncertain.

- You probably heard that Lyumjev or Fiasp are in principle *) best for looping.

   *) from an activity kinetics standpoint. References:
   figure S2 in https://github.com/bernie4375/HCL-Meal-Mgt.-ISF-and-IC-settings/blob/FCL-w/autoISF/**The**%20**Artificia**l%20**Pancreas**%20**and**%20**Meal**%20**Control.**pdf, and also
   https://github.com/bernie4375/FCL-potential-autoISF-research-/blob/FCL-book-autoISF/**Case**%20**Study**%201.2_**Insulins**%20for%20FCL_V2.1.pdf .

   In section 1.2.1 it is explained why it is a good idea to switch at the start of your looping journey, rather than at some later point.

   Changes between insulins with similar time-to-peak, like Fiasp -> Lyumjev, will be easier, and will not require much of an adjustment as in the example given in section 1.2.1.

41 But of course you can switch at any later time, as well. Many prefer actually to start
42 looping with a less reactive insulin. This enhances safety in the initial months of
43 getting to know, and tuning, the loop. (Same thought is behind the Objectives in
44 AAPS that give access to SMBs only after a couple of other steps).

45 Also, struggling with too many occlusions (and pain) can make it difficult to switch to one of the
46 fastest insulins.

47

1. Setting insulin related parameters

49 Besides time-(minutes) to-peak activity, also the duration of insulin action (DIA, hours) that
50 you select in your profile strongly influences how the loop calculates the activity from insulin,
51 as it unfolds in every 5-minute segment that your loop analyzes.

1.1 Mathematical model used

53

54 Especially what should be selected as duration of insulin action (DIA) is very strongly
55 influenced by the model used to figure out active insulin two, three, and more hours after
56 administration. Misunderstandings about this is often a source for disputes between loopers
57 and their treating physicians.

58 All insulin administrations (bigger and minor) add up to a insulin activity pattern.   In
59 the case of looping, with user boli, basal insulin, TBR modifications and SMBs given
60 at various times, with overlapping DIAs, this can be quite complex.

61 In AAPS you can see insulin activity in your main screen as an extra thin yellow
62 curve. Together with carb absorption is "explains" most of what you see in your
63 glucose curve.

64 This **insulin activity pattern is an extremely important basis for each of your**
65 **loop's decisions.** Having the wrong settings would give your semi-automated insulin
66 management a permanent drift towards over- or towards under-corrections.

67 The loop system can still counter-regulate, but – if you burden your's with wrong DIA
68 or time-to-peak settings in your profile – this would "use up" some of it's (limited)
69 capacity to regulate for you.

70 *Example: After heavy dinner, a DIA set <u>too short</u> "tells your loop" that active insulin is*
71 *practically gone after time X. The loop takes that info for granted, and if it sees some*

72   *insulin needed at that time X (and be it only for your profile basal need - as you also*

73   *communicate to the loop, you need to remain stable -), then, at night-time, the loop*

74   *will give you <u>more</u> insulin than you really need.*

75   *Therefore, before you tune your ISF differently, make sure to have a look at your DIA*

76   *setting.*

77 Please understand (and see to it, that your treating professionals understand) that models

78 can differ strongly:

79 •   DIY looping systems use the – less common – exponential decay model.

80 •   Medtronic uses non-linear capped curves (as in handbook to their pumps)

81 •   Doctors / diabetes educators mostly have a rough linear model in mind

82 •   xDrip uses a bilinear math ("with kinks") to model insulin activity (Caution: This info

83   might be outdated)

84 All models are working „good enough" for their (main) intended applications. But, as

85 explained above, it is worth the effort to use an exact modelling of insulin activity for a loop,

86 so it can perform optimally.

87 As pointed out already in the section 1 headline, and further explained below, the

88 mathematical model of insulin activity over time anchors on time-to-peak (minutes) and on

89 DIA (hours) in characteristic ways. This is quantitatively shown for exponential decay models

90 in [section 1.2.3-](#)

91 In AAPS, the insulin tab shows two curves:

92 The **pink** one starts at 1.0 (100%) and goes down to 0 (0%) when the DIA is over. It shows

93 how much of the total activity (the capacity to lower bg) is left, at any time. So, it is like the

94 iob number we always have in our AAPS home screen. The problem with that, as with the

95 pink curve, is that it may give you a false impression regarding how much "power" there

96 actually is, now, as you need it. That is where the other curve (and on your AAPS home

97 screen, the related thin yellow insulin activity curve) come in:

98 The **blue** one shows how the activity goes: Practically nothing (!) for a bunch of minutes,

99 then rapidly going high, and then slowly fading out out over the DIA period (with a maximum

100 at time-to-peak). For its calculations, AAPS adds these blue curves up for all boli, SMBs and

101 TBRs ≠ profile basal!

102

1.2 Time-to-peak activity and DIA for various insulins

104

105   Principally, there are „correct" settings specific for each insulin type, notably regarding time-
106   to-peak activity. This is pre-programmed in the insulin choices for AAPS, for instance.

107   Regarding the DIA to set, there is more uncertainty. The following mostly cites or
108   summarizes finings published by David Burren.

109   **1.2.1 Insulin choice matters for profile ISF, IC**

110   The following chart is *the inverse* of the pink curve in the AAPS insulin tab: *Not insulin still*
111   *there to be used*, but Insulin used up, going from 0% towards 100% in the 9 h DIA, for
112   Humalog with 75 minutes, and for Lyumjev with 45 minutes time-to-peak.

Insulin Used
BionicWookiee.com 2022
— Humalog 9h/75   — Lyumjev 9h/45

113
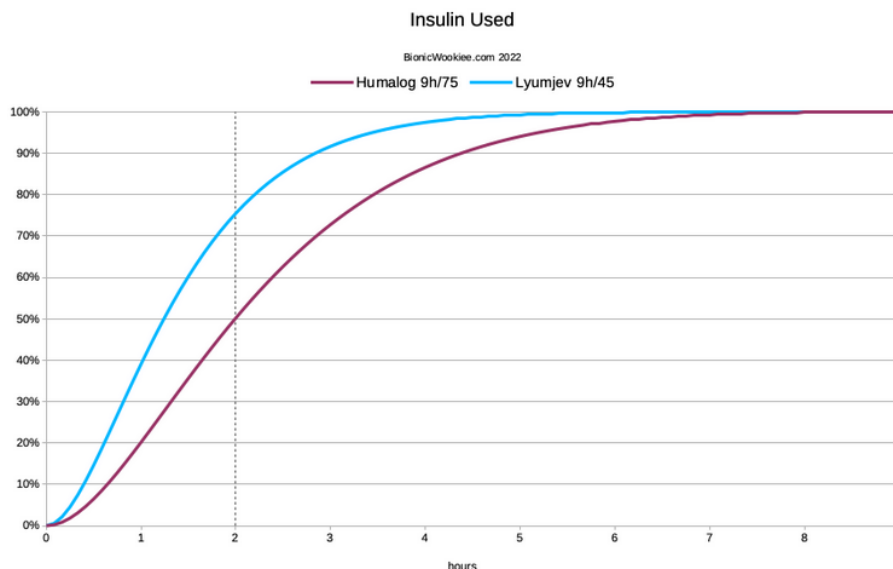
114   From a simplistic point of view, you can see that at the two-hour mark, more of the Lyumjev
115   (75.5%) should have had effect than the Humalog (50.2%).

116   So when we're calculating *how much insulin to give for a correction*, we should tell it to give
117   more Humalog up-front to get the same result after 2 hours.

118   "With the current incarnation of the oref1 algorithm I do find it helpful to scale the ISF (and IC)
119   relative to the amount of each insulin used in the first 2 hours. For Fiasp ~66% is used in the
120   first 2 hours. Lyumjev 75% (and NovoRapid/etc 50%).
121   Thus for Lyumjev I use ratios that are 15% larger than for Fiasp.
122   Basal rates are unchanged."   (D. Burren, AAPS Users 03Apr.2024)

123   The system will of course be tracking the IOB and forecasting the BG curves for hours
124   into the future, so we do have some safety built in regarding the extra insulin.

125 When going from Humalog to using Lyumjev, this must have some consequences for the

126 Insulin Sensitivity Factor (ISF) to use in the profile. If, for example, you had 1.8 mmol(l/U for

127 Humalog, you should expect a "good ISF for going with Lyumjev" in the area of 2.7 mmol/l/U.

128 According to the curves shown above (at dotted 2 hr line) a factor 75.5/50.2 applied yields

129 the same amount of insulin for a correction.

130 Likewise, the Carb Ratio (IC) may deserve an adjustment when switching insulins.

131 • The IC could be adjusted by the same factor, for instance it might go from 7.7 g/U
132 (Humalog) to 11.6 g/U (Lyumjev).

133 For a meal of 60 g, 7.8 U (=60/7.7 g/U) Humalog would have contributed 3.9 U
134 (=50.2%*7.8 U); likewise, 5.2 U (=60g/11.6 g/U) would have contributed 3.9 U
135 (=75.5%*5.2 U)

136 • For meals bigger than about 60 g you should observe that, while your insulin bolus has good
137 activity, only a limited number of carbs can get digested (30 g/h seems the limit for most).
138 Refer to the paper on IC determination (section "Determination at meal times") in:
139 https://github.com/bernie4375/HCL-Meal-Mgt.-ISF-and-IC-settings/tree/FCL-w/autoISF

140 The given example showed that switching to a "faster" insulin can have relevant

141 consequences for your key profile parameters.

142 David Burren also reports that between the two rather extreme insulin choices he tested, the

143 total amounts of insulin (TDD) did not significantly differ (- as we would expect: The same

144 amounts just gets delivered slower, even at same selected DIA, with Humalog).

145 But while the TDD has *not* changed, the instantaneous insulin levels *have*.
146 When the system is fighting post-meal "highs" the IOB will be noticeably lower with Lyumjev.

147 Although the average overall level remains similar, this might have some implications
148 for the concept of hyper-insulinaemia. This may be a subtle advantage of faster
149 insulins.

150 1.2.2 Duration of insulin action

151 The following focusses on the more uncertain topic of which duration of insulin action (DIA)

152 to use. It is largely relies on, and quotes, results from several thorough investigations done
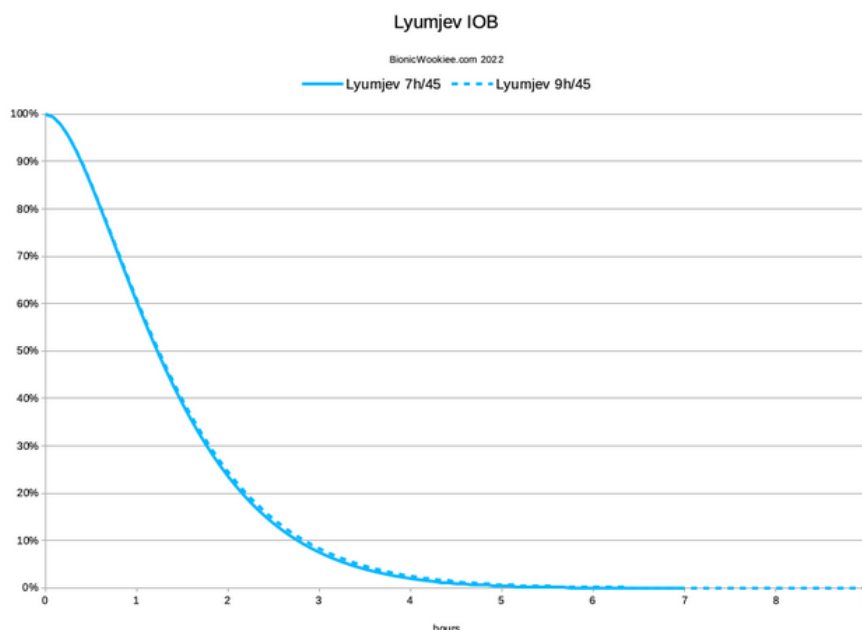
153 by David Burren: (https://bionicwookiee.com)

154 The numbers he ended up preferring are:

Insulin	Peak	Duration (DIA)
Humalog	75 minutes "Rapid-Acting Oref"	7 hours *)=
NovoRapid	75 minutes "Rapid-Acting Oref"	9 hours
Fiasp	55 minutes "Ultra-Rapid Oref"	9 hours

155 *) Later investigations https://bionicwookiee.com/2022/04/13/revised-humalog-model-in-a-closed-loop/
156 led to suggesting 9 hours DIA also for Humalog

157 The default constraints in AAPS have the duration limited to 7 hours, so he had to
158 make some local changes to the limits. It's also possible if you set your "patient type"
159 to "Pregnant", but if so you need to carefully check all the affected safety limits (listed
160 in the AAPS documentation). This may change in a future update to AndroidAPS.

161 For Lyumjev (45 minutes; Lyumjec Oref), there is not a big difference between a 7 and a 9 h
162 DIA:

163

164 However, David Burren (https://bionicwookiee.com/2022/04/13/revised-humalog-
165 model-in-a-closed-loop/) reports that, despite it's a very subtle change, he has found
166 it can make a significant difference 5-6 hours after a meal, when …the tails of the
167 earlier doses do add up, and the system had been underestimating the IOB when
168 calculating (using the shorter DIA) what was needed with new doses. With changing
169 to a longer DIA, his average Time Below Range has reduced. (Comment: This is

170   interesting for "fine-tuning extremists" but probably only a formal gain of little clinical
171   significance, assuming the bg curve just swinging a bit more often, or longer, by a few
172   mg/dl below the 70 mg/dl cut-off, that defines "below range". Judge from your own
173   data, when/if fine tuning.)

174 On the DIA topic for various insulins see also: https://www.diabettech.com/insulin/why-we-
175 are-regularly-wrong-in-the-duration-of-insulin-action-dia-times-we-use-and-why-it-matters/

176

177 1.2.3 Quantitative effects of changing DIA

178

179 Any given insulin dose comes with a defined total capacity for a certain bg lowering effect.
180 How strong or weak this unfolds over a couple of hours can be mathematically modelled.
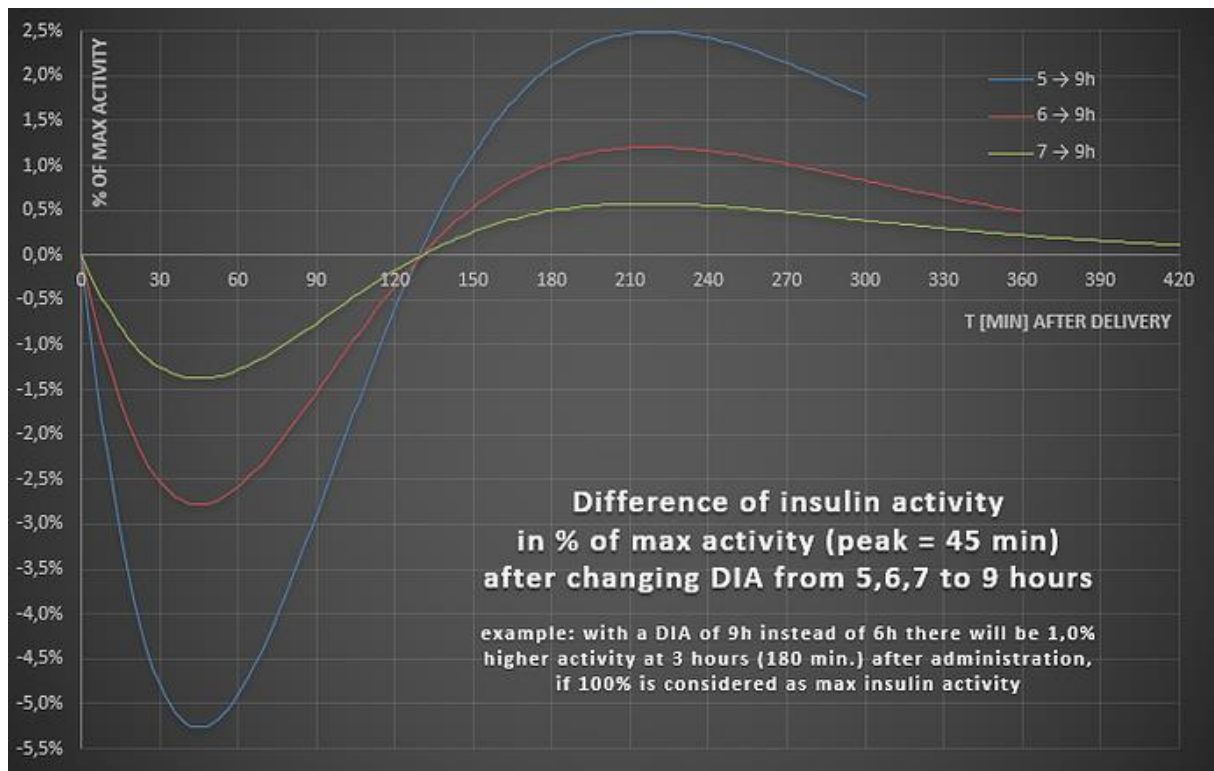181 In oref(1) systems, time-to-peak and DIA completely define this curve.

182 We can look on effects of increasing the set DIA in terms of how insulin activity would differ
183 at any moment after administering a dose.

184 The next example given (chart below) does that for going from a 5 h DIA, a 6 h DIA or a 7 h
185 DIA towards 9 h for Lyumjev

186 We see the peak going lower, and the tail activity higher when DIA is increased:

187

188 **LYUMJEV**   peak @45m   max effect on "tail" at ~ 3.5 h (220 minutes)
189 DIA 5→9h | **minus 5.5 %**   **plus 2.5%**
190 DIA 5→6h | minus 2,7 %   plus 1.3%
191 DIA 6→9h | **minus 2.8 %**   **plus 1.2%**
192 DIA 6→7h | minus 1,4 %   plus 0.6%
193 DIA 7→9h| -   **minus 1.4 %**   **plus 0.6%**
194 So, the „tail" effects differ by less than 3 percent (of peak activity=100%) in the later stages of
195 DIA:

Difference of insulin activity
in % of max activity (peak = 45 min)
after changing DIA from 5,6,7 to 9 hours

example: with a DIA of 9h instead of 6h there will be 1,0%
higher activity at 3 hours (180 min.) after administration,
if 100% is considered as max insulin activity

196

197   While 3 % sounds low, the significance of the problem should not be underestimated:

198   • For our Lyumjev case, note that the quoted 3% result is *3% of maximal activity.*
199   *Example: Activity at 180 minutes is about 0.0010 compared to 0.0080 at peak (blue*
200   *curve in AAPS INS tab). 2.5% of 0.0080 would be 0.0002. BUT: 0.0012 is 20 %*
201   *more than 0.0010, so* **REALLY the difference in activity at 180 minutes can be up**
202   **to 20%** *. Still, after a bolus of 8 units (and/or SMBs that reach that iob level) for a*
203   *typical meal, the max. difference from 5 -> 9 hour DIA would roughly be, whether 1.0*
204   *U or 1.2 U are active iob left at 180 minutes.* That **difference (+ 0.2 U)** should be
205   within the loop's regulating capacity from reducing basal.
206   However,it becomes much bigger for users of other insulins (with longer time-to-
207   peak):

208

209   • The delta **effects get much bigger with insulins that have a longer time-to-peak**
210   Some quantitative data for other insulins are as follows:

211   **FIASP** (peak=60m)   min/**max** differences
212   DIA **5→9h** | 6→9h | 7→9h: -10,1 **/ +6,8%** | -5,6 / +3,0% | -2,9 / +1,4%

213

214   **NOVORAPID** (peak=75m)   min/**max** differences
215   DIA 5→9h | 6→9h | 7→9h: -15,4 **/ +14,1%** | -9,1 / +7,0% | -4,8 / +3,0%

216

217   *Above example applied to Novorapid **):* The effect would be up to +14.1% *of max (!)*

218   => 2.1 U instead 1 U at 180 minutes. A ***difference of + 1.2 U*** results here, if DIA is

219   set at 5, not at 9 h, so **REALLY** it could go **up to + 120%** !)

220   More see: szantos, de.loopercommunity.org   May 2022

221   https://de.loopercommunity.org/t/naechtlicher-unterzucker/10626

222   **) 2,5% → + 0.2 U ergo 14.1% → +1,1 U stimmt insofern nicht ganz genau, als man beim
223   Novorapid Case auch die Novorapid Peak-Höhe zugrunde legen müsste (die ich aber nicht
224   greifbar habe). Wenn diese von Haus aus 20% niedriger nur kommt, hätten wir ca + 0,9U, also
225   weiterhin etwa eine Verdoppelung … die wir mit unserer Wahl eines längerem DIA unserem
226   Loop sagen könnten, damit er entsprechend weniger zu-schiesst … ergo weniger Hypogefahr
227   hinten heraus …

228

229   1.2.4   Shorter time-to-peak allows better control of meal-related bg spikes

230 A modelling study „The Artificial Pancreas and Meal Control" by A. El Fathi et al (ref.1) can
231 help us understand the effects on glucose peak heights from the course of carb absorption and
232 of insulin activity. The graph shows on the y axis peak over baseline (the overall deltaBG in
233 mmol/l), and on the x-axis the relative speed of insulin absorption to carb absorption. Carb
234 absorption is always faster, therefore all values are under 1.0. But with Lyumjev we move
235 closer to 1. The model calculation shows that **faster insulins** (red dotted) will result in **lower**

glucose **peaks** than slower insulins (violet dotted: reduction by 46% or minus 2.5 mmol/l =

minus 46 mg/dl after a 60 g carb load).

So, this model supports that using a faster insulin will

- lead to less high glucose peaks, notably for bigger meals

- or might **tolerate** a couple of minutes **delayed** first meal bolus while not incurring unacceptable height of peaks.
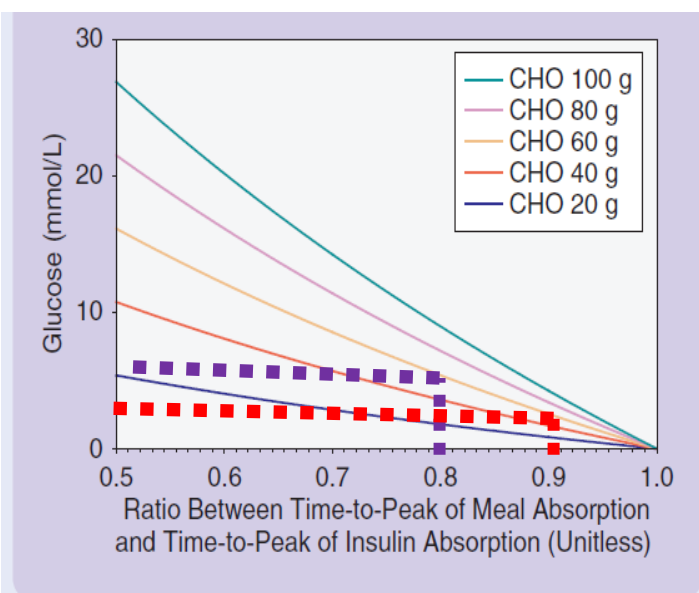
FIGURE S2 A plot of the maximum glucose peak after ingestion of different carbohydrate (CHO) quantities as a function of the ratio between time-to-peak of meal absorption τ_m and time-to-peak of insulin absorption τ_i. This graph shows that, for instance, following a 60-g meal, the maximum peak of glucose is 5.4 mmol/L for a ratio $\alpha = \tau_m/\tau_i = 0.8$. Increasing the ratio to 0.9 (by slowing the meal digestion or providing a faster-acting insulin) may result in decreasing the peak by 46% to 2.5 mmol/L.

The latter is a pre-requisite for full closed loop, in which we leave it up to the loop to notice that a meal „must have started", and to come forward with SMBs that are typically delayed compared to the bolus as given in hybrid closed loop.

This is an encouraging result.

251

252

253

254 mmol/l (+70 mg/dl) when using a faster insulin with factor 0.9, which, when starting at or
255 under 110 mg/dl, could keep glucose in range.

256 The message we can take from this is: **The higher carb loaded our diet, the more**
257 **important to use the fastest-available insulin.**

258

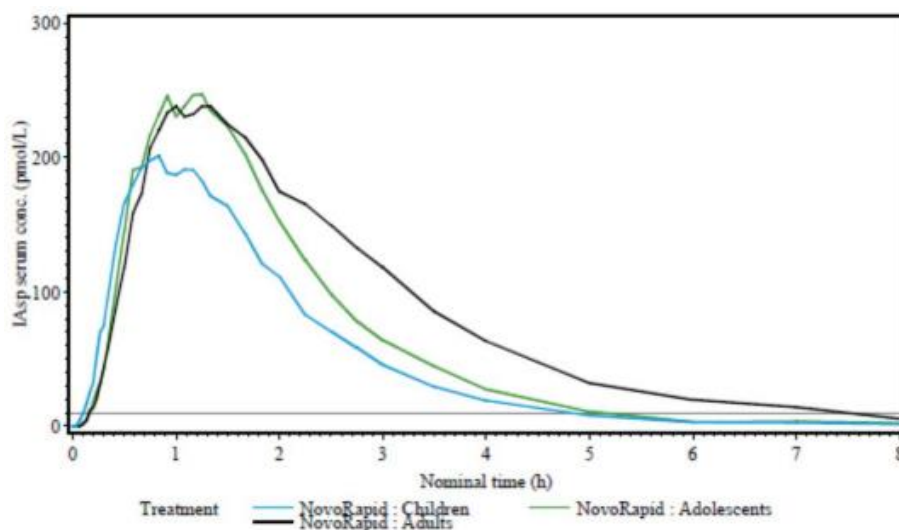## 2. Other factors of potential relevance
259 *Source:* szantos

260 The findings reported below can give you hints in which direction to look if you attempt to
261 fine-tune your settings further, from the standard suggestion what should be suitable for your
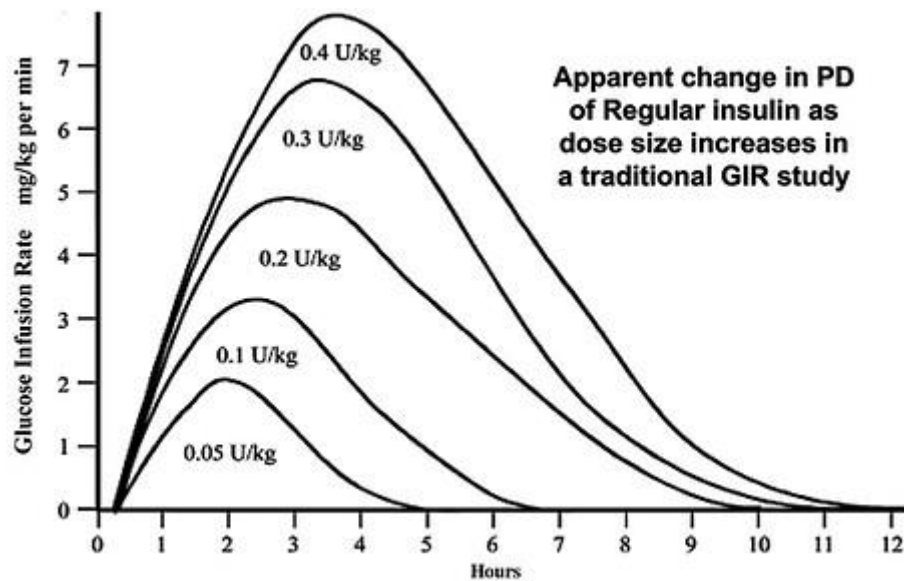262 insulin (section 1.2.2.).

2.1 Age (of the diabetic)
263

264 ema.europa.eu

265 **novorapid-h-c-258-p46-0044-epar-assessment-report_en.pdf 3**

266

267

268

269

2.2 Dose
270

271
272 https://journals.sagepub.com/doi/10.1177/1932296813514319

Apparent change in PD
of Regular insulin as
dose size increases in
a traditional GIR study

273
274 image1000×632 78.4 KB
275
276

2.3 Scatter (imprecision)

278

Individual deviations from standard suggestions could also be justified by the fact, that all
studies that underly the previously reported suggestions, come with very significant person-
to-person scatter.

All lines in the charts, as above shown from studies, are averaged data. (Some studies are
indicating the very significant scatter seen, as well).

https://www.researchgate.net/figure/Pharmacodynamic-profiles-Insulin-action-as-expressed-
as-GIR-required-to-maintain_fig1_41424712 2

3. Mixes of two insulins

The author did for some time successfully use a 50/50 mix of Fiasp and Novorapid, applying the time-to-peak for Fiasp, and longest of the two DIA, as was suggested at the time, for these insulins.

For a more thorough discussion see https://bionicwookiee.com/2022/03/02/mixing-insulins-theory-and-practice/

and also: https://bionicwookiee.com/2023/06/03/arcane-lyumjev-experiments/

4. U200 insulins

Using up-concentrated insulins, e.g. in a U200 form, is sometimes chosen by loopers

- to reduce needed daily insulin volumes and get more time from 1 pump filling (pod)
- to reduce volume per injection for getting better tolerance regarding occlusions or pain

There are no relevant effects on insulin parameters like DIA and time-to-peak.

However, dilution or up-concentration factors are highly relevant for setting profile factors like ISF and IC, and also for some important safety settings like max iob for instance.

Refer to special discussions on that topic, e.g. here re. U200 Lyumjev
https://www.diabettech.com/lyumjev/living-with-lyumjev-almost-a-year-in-review/ :

and also: https://bionicwookiee.com/2023/06/03/arcane-lyumjev-experiments/

5. Complementary utilization of insulins with super fast bio-availability

The effect of time to peak activity on bg control was shown quantitatively in the study presented in section 2.1.4. It is the core problem coming with any sub-cutaneous insulin provision (via sub-cutaneous injections, or via insulin pumps), that time-to-peak activity can be rather long.

In the following we touch on faster ways to get insulin into blood. **Please note that the author does not encourage you to try any of those** unless in a medically supervised study context. Also, be aware that faster acting insulins further increase danger of hypoglycemia.

5.1 Using i.v. insulin

The "beauty" of using intra-venous insulin at around meal starts would stem from its much faster bio-availability, and also much shorter DIA

Case report: I do a basically unknown amount of insulin intravenously, let it be between 4 and 8 units (well below the size that my meal bolus would be). It really doesn't matter anyhow. What it does ,it brings me down to target within 30-40min. I record something like 4-6 units (so my loop doesn't want to get excessive insulin). Essentially, this prevents getting insulin longer than it actually has an effect (mine is gone from the system after 35min). To eliminate the false "activity tail" assigned also to the i.v. potion of insulin on bord, you can delete the i.v. insulin amount from the system *after it has done it's job* (not good for statistics/history data, but right, going forward without the DIA tail = letting your loop know the real iob).

It's an edge use (experimental) case .   (source: Robert, discord FCL/iaAPS w autoISF, March 2024):

Please observe that this is not a recommendation to experiment with i.v. insulin unless in a medically supervised research context.

i.v. insulin is usually restriced to the surgical and intensive care hospital environments!

5.2 Inhaled insulin (Afrezza)

Afrezza is an inhaleable very fast (and also short) acting insulin which some find useful to correct high glucose levels.

> Pro: An insulin inhalation addresses the need for a fast correction of a bg high, and even without the hours-long tail of effects.

> Cons: 1) Afrezza spray is hard to dose. 2) Also it is not advisable to enter data into loop because the kinetics of this insulin are very different. => The short term problem is solved, but there are consequences in the upcoming hours from skewed calculations and eventually also (via Autotune-driven basal and factor adjustments) for the next days. ((Could partially be resolved if insulin unit equivalents coming from Afrezza are entered at bolus time, and then erased, as soon as it's activity is over)).
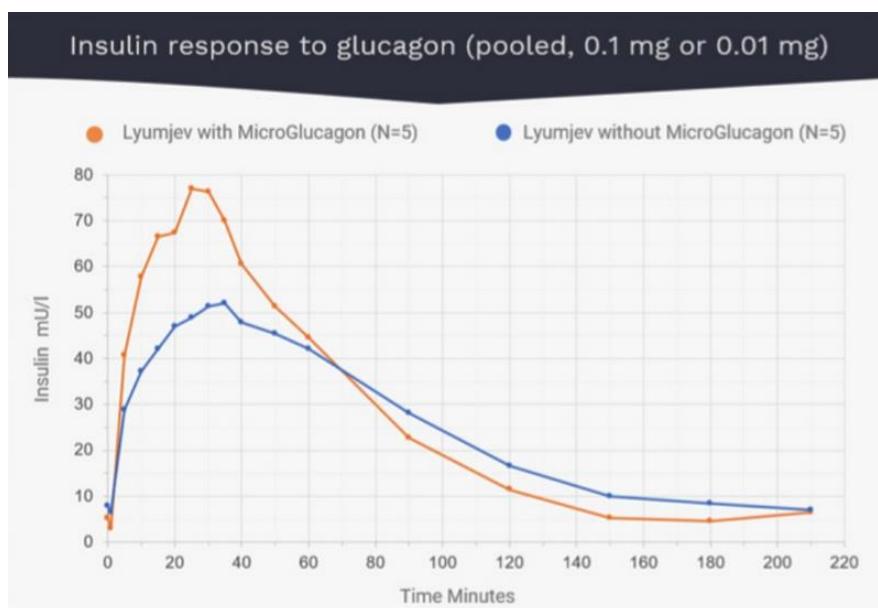
349　　　　3) Primary approach should be to avoid high bg by finding a proper meal

350　　　　management strategy (pre-bolus time, EatingSoonTT).

351　Still Afrezza can be a reasonable remedy in times. Solving the problem at hand as best as

352　we can, even if it makes the time afterwards a bit more complicated, is the name of the

353　game. We and our loop do this all the time, for instance by giving more upfront insulin, then

354　reducing basal (zero-temping).

355　　　(from slide 38 of: Meal Mgt. Basics, https://github.com/bernie4375/HCL-Meal-Mgt.-

356　　　ISF-and-IC-settings)

357

358　**5.3 Lyumjev + microGlucagon mix**

359　A highly experimental approach to further improve the kinetics of Lyumjev fro looping has

360　been researched by a T1D physician (Dr. Carlsen, Trondheim, Norway) in self-experiments,

361　with some promising first results.

362

363

364　Full article from Norwegian hospital researchers group:

365　https://norwegianscitechnews.com/2024/01/a-new-insulin-mixture-could-make-life-easier-for-

366　patients-with-type-1-diabetes/

367

368　See also related discussion in "AAPS Users" FB (Alf Einar Johnsen**,** Jan 19, 2024)
369　https://www.facebook.com/groups/AndroidAPSUsers/permalink/373300573587499/?mibexti
370　d=W9rl1R

371　… and in "iAPS unchained" FB (Robban Jansson, 06 May, 2024)
372　https://www.facebook.com/groups/151989761311250/permalink/286074914569400/