COMMENTARY

Ongoing Debate About Models for Artificial Pancreas Systems and In Silico Studies

Gregory P. Forlenza, MD

IT IS WITH great pleasure that I agreed to provide clinical perspectives and commentary on the issues raised by Garry Steil, PhD regarding the best use of models to advance artificial pancreas (AP) systems. Respectful and constructive academic debate on these fundamental issues serves to refine our thinking and educate the broader audience, provided that such debate does not stifle continued medical advancement. Indeed, much of my understanding of the algorithms behind emerging AP systems was gained by reading Dr. Steil's original debate with B. Wayne Bequette, PhD on the cases for proportional-integral-derivative (PID) control and model predictive control (MPC).^{1,2} This initial debate occurred in 2013 at a time when many AP systems were still laptop based, and before the publication of any 24-h home-use AP trials. Contrast this to the current environment where the first hybrid closed loop (HCL) AP system is now in routine clinical use,^{3,4} although numerous others are in commercial development,^{5,6} and we see that the landscape has evolved dramatically over the intervening 5 years. The issues raised by Dr. Steil in his commentary relate to the optimal control strategy for AP systems as well as preclinical testing of evolving controllers given the current and rapidly evolving diabetes technology landscape.⁷

The control algorithm in an AP system is the behind-the-scenes "brains" of the system linking the glycemic measurement of the continuous glucose monitor (CGM) with the insulin delivery of the continuous subcutaneous insulin infusion (CSII) pump. The concepts behind the algorithms can be broken down into one of three main designs: PID, MPC, or fuzzy logic (FL) control, which have been fully described elsewhere.^{8–16}

The only commercially available AP system, the Medtronic 670G HCL AP, uses a PID-based controller along with an insulin feedback component.^{16,17} Other systems currently undergoing clinical trials use model predictive control-based controllers developed by Kovatchev, Breton, and Cobelli,^{12,18} Doyle and Dassau,^{19,20} Hovorka,^{10,21} and Damiano.^{22,23} An FL-based system by Phillip and Atlas is also undergoing trials.¹⁴ Although this list is not exhaustive, and work is ongoing by numerous other groups, it serves to show that a wide array of AP algorithms are currently under development and that the majority of these are MPC in design. It is not

clear why MPC appears to be favored, although it may be due to MPC's ability to handle additional inputs beyond glucose and insulin infusion rates (e.g., insulin on board or exercise data) or MPC's ability to consider events that are a function of time.²

There continues to be substantial debate about which form of controller design will be better for AP system use in type 1 diabetes (T1D) patients. In their original debate, both Dr. Steil and Dr. Bequette emphasized that there are many different forms of PID and model predictive controllers and that different designs may result in different tradeoffs of benefits and deficits for different scenarios.^{1,2} A major point at that time was that no head-to-head studies of different controllers had been conducted. Then in 2016, Pinsker published the results of a randomized crossover trial comparing a PID controller with an model predictive controller, both designed by the Doyle/Dassau group.²⁴ They found that their model predictive controller produced significantly greater time in target range (70–180 mg/dL) than their PID controller (74.4 vs. 63.7%; $P=0.020$), with lower mean glucose (138 vs. 160 mg/dL; $P=0.012$), and without a statistically significant difference in time <70 mg/dL (4.6 vs. 2.9%; $P=0.329$). This study subsequently concludes that "MPC performed as well or better than PID in all metrics." The results from this study produced another stimulating and educational academic debate between Dr. Steil²⁵ and the Pinsker/Doyle/Dassau group,²⁶ wherein the authors discuss the importance of iterative testing and tuning of AP systems and the challenges in establishing the correct level of system aggressiveness across different clinical scenarios.

Additional comparison of controller designs can be seen in the AP meta-analysis by Weisman et al.⁵ In this meta-analysis they analyze 27 comparisons from 24 randomized controlled studies. They report that the mean difference for percentage time in the range between AP and conventional therapy for MPC was 14.3% and that for FL was 16.49%, both a significant improvement ($P<0.0001$), whereas for PID it was 6.97% and not statistically significant ($P=0.11$). Hypoglycemia reduction (% <70 mg/dL) for MPC was –1.95% and that for FL was –2.45%, both significant ($P\leq 0.001$), whereas that for PID was larger at –3.98%, although not statistically significant ($P=0.21$). It could be argued that the

MPC trials ($n=15$) were better powered within the meta-analysis than the PID trials ($n=9$), although the FL trials ($n=3$) showed statistical significance with the smallest overall number of trials.

From a clinical perspective, however, the question of controller design is quite different, relating to ease of understanding and ease of use for providers and patients. Challenges in clinical understanding and implementation of a wide array of AP designs are just coming to the clinical forefront, and are likely to get worse as additional systems become clinically available.²⁷ In clinical practice, MPC designs present a distinct advantage over PID designs due to their use of preprogrammed basal rates as an input. Model predictive controllers generally work by modulation of a patient's preprogrammed basal profile, whereas PID controllers use only total daily dose to individually tune basal insulin delivery. Clinically, use of basal profiles as a controller input allows providers and patients a degree of control in tuning system aggressiveness at various times of day. Previous research has shown that basal patterns show significantly different profiles based on age, and within different age groups there are distinct peaks and troughs basal rates in a diurnal pattern beyond the simple "dawn phenomenon."^{28,29}

Basing control on known basal patterns presents a significant advantage for certain patient populations, wherein it is known, or highly expected, that there will routinely be differences in background insulin needs at different times of day. Examples of this include (1) toddlers wherein it is known that insulin requirements increase dramatically after bed due to nocturnal growth hormone release and then drop significantly in the early morning, (2) young adult athletes who routinely engage in aerobic activity at a given time of day, and (3) shift workers who may alternate between basal patterns based on being awake during the day or at night. Although it is true that a proportional and derivative controller may substitute basal rates for the integral term, such a design is not currently undergoing commercial trials. Future system designs may "auto-tune" settings for AP as well as open-loop CSII pumps, and even patients using multiple daily injection.³⁰ However, for early generation AP systems, ability to input and manually tune basal rates as a system input is likely to aid experienced patients and providers in uptake and utilization of this evolving technology.

Preclinical testing of emerging AP algorithms has been aided over the past decade by the Food and Drug Administration (FDA)-approved UVA/Padova T1D simulator.^{31,32} Serving as a substitute for timely and costly animal studies, the simulator allows for preclinical assessment of certain insulin treatment strategies and closed-loop algorithms. As of 2014, the simulator had been used by 23 different research groups, resulting in 63 publications in peer-reviewed journals.³² The original simulator was designed in 2008 and was updated in 2013 to account for "nonlinearities of insulin action and glucagon kinetics in the hypoglycemic range." The UVA/Padova simulator has since been validated in a clinical study³³ in addition to its wide usage by a diverse number of groups. However, failure of the simulator to account for variability of insulin sensitivity within a given patient has also been cited as a significant limitation of the simulator. Fortunately, Cobelli and colleagues are addressing this limitation and have published analysis of additional features incorporating diurnal variability of glucose absorp-

tion and insulin sensitivity, allowing for more feasible week to month-long simulation of T1D control.³⁴ Discussion of these changes highlights two aspects of the UVA/Padova simulator as a tool for developing AP systems: (1) as with any new and rapidly changing technology, it contains flaws and imperfections and (2) its flaws have been and are continuing to be acknowledged and addressed by the designers in an iterative and constructive manner.

The final point raised by Dr. Steil in his commentary is an exciting one: "Given what we currently know about the safety and performance of AP systems ... neither preclinical animal studies nor model simulations should be required prior to conducting an in-patient clinical study." Although the UVA/Padova simulator serves as an excellent tool to rapidly advance technology while protecting patient safety, any model-based simulator will be limited by our own understanding of a condition as complex and multifactorial as T1D. Given the significant advances in CGM technology and with appropriate in-patient supervision by trained study staff and investigators, supervised studies can be conducted with less risk than most outpatient T1D management. The challenge could potentially come with rare "edge cases" in algorithm performance, which may be unlikely in a hospital-based environment, but which may be identified with robust in silico testing. Risk from such cases could still be mitigated, however, with rigorous staff and subject training, redundant safety precautions, and remote monitoring for early phase human studies. As such, it may now be the time for the FDA to re-evaluate the need for simulation or animal studies of control algorithms in certain circumstances.

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Address correspondence to:
 Gregory P. Forlenza, MD
 Barbara Davis Center
 University of Colorado Denver
 1775 Aurora CT
 MS A140
 Aurora, CO 80045

E-mail: gregory.forlenza@ucdenver.edu