Displacement Micropump with Check Valves for Diabetes Care—The Challenge of Pumping Insulin at Negative Pressure

Subjects: Engineering, Biomedical | Medical Laboratory Technology

Contributor: Eric Chappel

The displacement micropump with passive check valves is an attractive solution for precise insulin infusion in patients with type I diabetes. Unlike most insulin pumps that push insulin from a cartridge using a piston, a displacement micropump will first pull insulin from the reservoir before infusing it into the patient. This dual sequence introduces new challenges in terms of insulin stability, notably if the reservoir is not pressurized. After an introduction to displacement micropumps and a brief review of the insulin degradation mechanism, micropump design rules are discussed in light of microfluidic theory.

MEMS micropump | displacement pump | check valves | pump failure mode | insulin delivery | diabetes care

Diabetes is a chronic metabolic disorder characterized by high blood sugar levels that cause serious damage over time. Type 1 diabetes, also called insulin-dependent diabetes, is a condition in which little or no insulin is produced by the beta-cells of the pancreas. Daily administration of insulin is essential to the survival of people with type 1 diabetes.

Traditionally, insulin is administered by subcutaneous injection using an insulin syringe or pen. Advanced insulin delivery systems include patch pumps which administer fast-acting insulin 24 h a day to meet the body’s needs, via a fine cannula placed subcutaneously. Continuous subcutaneous insulin infusion (CSII) has proven to be effective in diabetes care [1][2][3][4][5][6][7]. These programmable pumps can deliver both basal and bolus doses of insulin. Basal insulin delivery rates are programmed by the physician to meet individual patient needs. Insulin pumps can also deliver bolus insulin to minimize blood glucose deviations after meals. The recent improvement in blood glucose meter accuracy enabled closing the loop thanks to specific algorithms and wireless communication between a continuous glucose meter and the delivery system for one (insulin) or two hormones (insulin and glucagon) [8][9][10][11][12]. Most commercially available insulin pumps feature a piston mechanism connected either to an insulin infusion device or to a cannula patch and occlusion detection system [13][14][15]. The accuracy of bolus and basal rate delivery, in nominal conditions, showed globally good results in agreement with the manufacturers’ specifications [16][17]. Larger deviations are observed at short observation windows (typically less than 1h in basal rate), due to the inherent noise induced by the pumping engine itself and the so-called stick–slip effect of the piston against the internal wall of the insulin container [18][19][20]. Other insulin pump designs have been studied to improve short-term variability of insulin delivery and shorten occlusion detection time [21][22][23][24]. Indeed, insulin delivery systems are designed to detect occlusion, which consists of a partial or complete blockage of insulin delivery, by monitoring the in-line pressure. Occlusion detection is crucial to maintain the blood glucose level in an acceptable range [25]. However, despite improvements in the catheter design to reduce the occurrence of silent occlusion [26], this failure mode remains difficult to detect, especially at low flow rates, as in-line built-in pressure increases slowly over time. Median occlusion detection times (ODT) at 0.1 U/h ranging from 4 h to more than 40 h in commercial insulin pumps were reported [27]. Occlusion may occur shortly after insertion of the infusion set, but generally increases after 2 or 3 days of use. The effect can be related to a kinking of the catheter or the soft cannula, a cannula leakage, the chemical precipitation of insulin, or the fibrin formation at the needle tip [28].

Depending on whether the externally applied energy is converted into fluid kinetic energy, micropumps can be categorized as nonmechanical or mechanical micropumps. These later devices are usually further divided into displacement or dynamic micropumps depending on whether mechanical energy is periodically or continuously transferred to the working fluid [21][29][30][31][32][33][34].

The focus here is on displacement micropumps with flow rectifiers, in which a force is applied periodically to one or more moving boundaries, which in turn exert pressure on the working fluid. Flow rectifying elements are implemented to prevent back-flow and free-flow. Insulin delivery systems with displacement MEMS (micro-electro-mechanical systems) pumps with passive check valves have indeed demonstrated interesting features in terms of occlusion detection and delivery accuracy [23][35][36][37][38][39][40][41]. Numerous actuation mechanisms were associated with this micropump structure, including piezoelectric [40][41][42][43], electrostatic [44][45], ionic conductive polymer film [46], thermopneumatic [47], electromagnetic [48], shape memory alloy [49][50][51], and bimetallic actuators [52].

Such a displacement pump engine is connected to the insulin reservoir and either an infusion set or a cannula that is directly inserted into the skin (patch pump). Sensors can monitor the pressure to detect any events that may induce over- or underdelivery. For basic safety reasons, the pressure relative to the atmosphere in the insulin reservoir is generally zero or slightly negative. During the filling phase of the pumping cycle, a negative pressure is generated in the pumping chamber to open the inlet valve and draw insulin from the reservoir. The fact that the insulin experiences a negative pressure is a significant difference from other insulin delivery systems, except the implantable pump MIP developed by Minimed to infuse U400 insulin via the intraperitoneal route [22]. The pressure of the MIP reservoir is −275±70

mbar to prevent the risk of overdose induced by leakage and the risk of pocket fill [53][54][55][56]. Most infusion systems are piston pumps that simply push the insulin present into the reservoir to the patient. To illustrate the difference between the two systems, the presence of air in the insulin reservoir is considered. Except in the case of prefilled cartridges, it is difficult to avoid the presence of air, especially if insulin, before being injected into the reservoir, is first extracted from a vial by the patient using a syringe. Air bubbles in a piston pump reservoir can generate an overdose in the event of depressurization (e.g., in an airplane) [22][57]. In the reservoir of a displacement pump with check valves, air can block the valves due to capillary effects and degrade delivery accuracy if air remains in the pumping chamber. The risks for the patient are therefore radically different: over- or underdelivery.

To tackle the challenges of infusing insulin with a displacement pump having check valves, a brief description of the pumping mechanism is first presented, together with an analysis of the link between design, pumping performances, and rapid occlusion detection. The compatibility of this pumping mechanism with the fragile insulin molecule is then reviewed in detail, with a comprehensive analysis of the failure modes. Finally, some insights about the design rules that can be implemented to improve the displacement micropump reliability and thus mitigate the risks associated with this pumping mechanism are presented.

References

1. Pickup, J.C.; Keen, H.; Parsons, J.A.; Alberti, K.G. Continuous subcutaneous insulin infusion: An approach to achieving normoglycaemia. Br. Med. J. 1978, 1, 204–207.
2. Bode, B.W.; Steed, R.D.; Davidson, P.C. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. Diabetes Care 1996, 19, 324–327.
3. Lenhard, M.J.; Reeves, G.D. Continuous subcutaneous insulin infusion: A comprehensive review of insulin pump therapy. Arch. Intern. Med. 2001, 161, 2293–2300.
4. Misso, M.L.; Egberts, K.J.; Page, M.; O’Connor, D.; Shaw, J. Cochrane review: Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Evid.-Based Child Health A Cochrane Rev. J. 2010, 5, 1726–1867.
5. Bruttomesso, D.; Costa, S.; Baritussio, A. Continuous subcutaneous insulin infusion (CSII) 30 years later: Still the best option for insulin therapy. Diabetes/Metab. Res. Rev. 2009, 25, 99–111.
6. Priesterroth, L.; Grammes, J.; Clauter, M.; Kubiak, T. Diabetes technologies in people with type 1 diabetes mellitus and disordered eating: A systematic review on continuous subcutaneous insulin infusion, continuous glucose monitoring and automated insulin delivery. Diabet. Med. 2021, 38, e14581.
7. Dos Santos, T.J.; Campos JD, M.D.; Argente, J.; Rodríguez-Artalejo, F. Effectiveness and equity of continuous subcutaneous insulin infusions in pediatric type 1 diabetes: A systematic review and meta-analysis of the literature. Diabetes Res. Clin. Pract. 2021, 172, 108643.
8. Steil, G.M.; Panteleon, A.E.; Rebrin, K. Closed-loop insulin delivery—The path to physiological glucose control. Adv. Drug Deliv. Rev. 2004, 56, 125–144.
9. Hovorka, R. Closed-loop insulin delivery: From bench to clinical practice. Nat. Rev. Endocrinol. 2011, 7, 385–395.
10. Bally, L.; Thabit, H.; Hartnell, S.; Andereggen, E.; Ruan, Y.; Wilinska, M.E.; Evans, M.L.; Wertli, M.M.; Coll, A.P.; Stettler, C.; et al. Closed-loop insulin delivery for glycemic control in noncritical care. N. Engl. J. Med. 2018, 379, 547–556.

11. Bergenstal, R.M.; Garg, S.; Weinzimer, S.A.; Buckingham, B.A.; Bode, B.W.; Tamborlane, W.V.; Kaufman, F.R. Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. JAMA 2016, 316, 1407–1408.
12. Tauschmann, M.; Thabit, H.; Bally, L.; Allen, J.M.; Hartnell, S.; Wilinska, M.E.; Ruan, Y.; Sibayan, J.; Kollman, C.; Cheng, P.; et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: A multicentre, 12-week randomised trial. Lancet 2018, 392, 1321–1329.
13. Bombaci, B.; Passanisi, S.; Alibrandi, A.; D'Arrigo, G.; Patroniti, S.; Averna, S.; Salzano, G.; Lombardo, F. One-year real-world study on comparison among different continuous subcutaneous insulin infusion devices for the management of pediatric patients with type 1 diabetes: The supremacy of hybrid closed-loop systems. Int. J. Environ. Res. Public Health 2022, 19, 10293.
14. Freckmann, G.; Buck, S.; Waldenmaier, D.; Kulzer, B.; Schnell, O.; Gelchsheimer, U.; Ziegler, R.; Heinemann, L. Insulin pump therapy for patients with type 2 diabetes mellitus: Evidence, current barriers, and new technologies. J. Diabetes Sci. Technol. 2021, 15, 901–915.
15. Wong, E.Y.; Vadlapatla, R.; Morello, C.M. Diabetes type 1 and type 2—Insulin delivery systems. In Drug Delivery Devices and Therapeutic Systems; Academic Press: New York, NY, USA, 2021; pp. 475–489.
16. Leelarathna, L.; Roberts, S.A.; Hindle, A.; Markakis, K.; Alam, T.; Chapman, A.; Morris, J.; Urwin, A.; Jinadev, P.; Rutter, M.K. Comparison of different insulin pump makes under routine care conditions in adults with Type 1 diabetes. Diabet. Med. 2017, 34, 1372–1379.
17. Freckmann, G.; Kamecke, U.; Waldenmaier, D.; Haug, C.; Ziegler, R. Accuracy of bolus and basal rate delivery of different insulin pump systems. Diabetes Technol. Ther. 2019, 21, 201–208.
18. Borot, S.; Franc, S.; Cristante, J.; Penfornis, A.; Benhamou, P.Y.; Guerci, B.; Hanaire, H.; Renard, E.; Reznik, Y.; Simon, C.; et al. Accuracy of a new patch pump based on a microelectromechanical system (MEMS) compared to other commercially available insulin pumps: Results of the first in vitro and in vivo studies. J. Diabetes Sci. Technol. 2014, 8, 1133–1141.
19. Bissig, H.; Tschannen, M.; de Huu, M. Traceability of pulsed flow rates consisting of constant delivered volumes at given time interval. Flow Meas. Instrum. 2020, 73, 101729.
20. Thornton, J.; Sakhrani, V. How lubricant choice affects dose accuracy in insulin pumps. ONdrugDelivery Mag. 2017, 78, 32–36.
21. Chappel, E.; Dumont-Fillon, D. Micropumps for drug delivery. In Drug Delivery Devices and Therapeutic Systems; Academic Press: New York, NY, USA, 2021; pp. 31–61.
22. Chappel, E. Implantable drug delivery devices. In Drug Delivery Devices and Therapeutic Systems; Academic Press: New York, NY, USA, 2021; pp. 129–156.

23. Fournier, S.; Chappel, E. Modeling of a Piezoelectric MEMS Micropump Dedicated to Insulin Delivery and Experimental Validation Using Integrated Pressure Sensors: Application to Partial Occlusion Management. J. Sens. 2017, 2017, 3719853.

24. Chappel, E. Robust alarm design strategy for medical devices: Application to air-in-line detection and occlusion management. Glob. J. Eng. Technol. Adv. 2023, 16, 030–040.

25. Cescon, M.; DeSalvo, D.J.; Ly, T.T.; Maahs, D.M.; Messer, L.H.; Buckingham, B.A.; Doyle, F.J., III; Dassau, E. Early detection of infusion set failure during insulin pump therapy in type 1 diabetes. J. Diabetes Sci. Technol. 2016, 10, 1268–1276.

26. Gibney, M.; Xue, Z.; Swinney, M.; Bialonczyk, D.; Hirsch, L. Reduced silent occlusions with a novel catheter infusion set (BD FlowSmart): Results from two open-label comparative studies. Diabetes Technol. Ther. 2016, 18, 136–143.

27. Freckmann, G.; Kamecke, U.; Waldenmaier, D.; Haug, C.; Ziegler, R. Occlusion detection time in insulin pumps at two different basal rates. J. Diabetes Sci. Technol. 2018, 12, 608–613.

28. Deiss, D.; Adolfsson, P.; Alkemade-van Zomeren, M.; Bolli, G.B.; Charpentier, G.; Cobelli, C.; Danne, T.; Girelli, A.; Mueller, H.; Verderese, C.A.; et al. Insulin infusion set use: European perspectives and recommendations. Diabetes Technol. Ther. 2016, 18, 517–524.

29. Nguyen, N.T.; Huang, X.; Chuan, T.K. MEMS-micropumps: A review. J. Fluids Eng. 2002, 124, 384–392.

30. Laser, D.J.; Santiago, J.G. A review of micropumps. J. Micromech. Microeng. 2004, 14, R35.

31. Woias, P. Micropumps—Past, progress and future prospects. Sens. Actuators B Chem. 2005, 105, 28–38.

32. Amirouche, F.; Zhou, Y.; Johnson, T. Current micropump technologies and their biomedical applications. Microsyst. Technol. 2009, 15, 647–666.

33. Wang, Y.N.; Fu, L.M. Micropumps and biomedical applications–A review. Microelectron. Eng. 2018, 195, 121–138.

34. Bußmann, A.B.; Grünerbel, L.M.; Durasiewicz, C.P.; Thalhofer, T.A.; Wille, A.; Richter, M. Microdosing for drug delivery application—A review. Sens. Actuators A Phys. 2021, 330, 112820.

35. Van Lintel HT, G.; van De Pol FC, M.; Bouwstra, S. A piezoelectric micropump based on micromachining of silicon. Sens. Actuators 1988, 15, 153–167.

36. Maillefer, D.; Gamper, S.; Frehner, B.; Balmer, P.; Van Lintel, H.; Renaud, P. A high-performance silicon micropump for disposable drug delivery systems. In Proceedings of the Technical Digest. MEMS 2001. 14th IEEE International Conference on Micro Electro Mechanical Systems (Cat. No. 01CH37090), Interlaken, Switzerland, 25 January 2001; pp. 413–417.

37. Schneeberger, N.; Blondel, A.; Boutaud, B.; Chappel, E.; Maillefer, D.; Schneider, V. Disposable insulin pump-a medical case study. In Proceedings of the DTIP of MEMS & MOEMS, Montreux, Switzerland, 12–14 May 2004; pp. 25–27.
38. Schneeberger, N.; Allendes, R.; Bianchi, F.; Chappel, E.; Conan, C.; Gamper, S.; Schlund, M. Drug delivery micropump with built-in monitoring. Procedia Chem. 2009, 1, 1339–1342.
39. Chappel, E.; Mefti, S.; Lettieri, G.L.; Proennecke, S.; Conan, C. High precision innovative micropump for artificial pancreas. In Microfluidics, BioMEMS, and Medical Microsystems XII; San Francisco, USA, 2–4 February 2014; SPIE: Bellingham, WA, USA, 2014; Volume 8976, pp. 279–290.
40. Dumont-Fillon, D.; Tahriou, H.; Conan, C.; Chappel, E. Insulin micropump with embedded pressure sensors for failure detection and delivery of accurate monitoring. Micromachines 2014, 5, 1161–1172.
41. Bußmann, A.; Leistner, H.; Zhou, D.; Wackerle, M.; Congar, Y.; Richter, M.; Hubbuch, J. Piezoelectric silicon micropump for drug delivery applications. Appl. Sci. 2021, 11, 8008.
42. Junwu, K.; Zhigang, Y.; Taijiang, P.; Guangming, C.; Boda, W. Design and test of a high-performance piezoelectric micropump for drug delivery. Sens. Actuators A Phys. 2005, 121, 156–161.
43. Stehr, M.; Messner, S.; Sandmaier, H.; Zengerle, R. The VAMP—A new device for handling liquids or gases. Sens. Actuators A Phys. 1996, 57, 153–157.
44. Zengerle, R.; Ulrich, J.; Kluge, S.; Richter, M.; Richter, A. A bidirectional silicon micropump. Sens. Actuators A Phys. 1995, 50, 81–86.
45. Uhlig, S.; Gaudet, M.; Langa, S.; Schimmanz, K.; Conrad, H.; Kaiser, B.; Schenk, H. Electrostatically driven in-plane silicon micropump for modular configuration. Micromachines 2018, 9, 190.
46. Guo, S.; Nakamura, T.; Fukuda, T.; Oguro, K. Development of the micro pump using ICPF actuator. In Proceedings of the International Conference on Robotics and Automation, Albuquerque, NM, USA, 25 April 1997; Volume 1, pp. 266–271.
47. Van de Pol FC, M.; Van Lintel HT, G.; Elwenspoek, M.; Fluitman JH, J. A thermopneumatic micropump based on micro-engineering techniques. Sens. Actuators A Phys. 1990, 21, 198–202.
48. Böhm, S.; Olthuis, W.; Bergveld, P. A plastic micropump constructed with conventional techniques and materials. Sens. Actuators A Phys. 1999, 77, 223–228.
49. Benard, W.L.; Kahn, H.; Heuer, A.H.; Huff, M.A. Thin-film shape-memory alloy actuated micropumps. J. Microelectromech. Syst. 1998, 7, 245–251.

50. Makino, E.; Mitsuya, T.; Shibata, T. Fabrication of TiNi shape memory micropump. Sens. Actuators A Phys. 2001, 88, 256–262.

51. Xu, D.; Wang, L.; Ding, G.; Zhou, Y.; Yu, A.; Cai, B. Characteristics and fabrication of NiTi/Si diaphragm micropump. Sens. Actuators A Phys. 2001, 93, 87–92.

52. Zhan, C.; Lo, T.; Liu, L.; Peihsin, T. A silicon membrane micropump with integrated bimetallic actuator. Chin. J. Electron. 1996, 5, 33.

53. Renard, E. Continuous intraperitoneal insulin infusion from implantable pumps. In Technological Advances in the Treatment of Type 1 Diabetes; Karger Publishers: 2015; Volume 24, pp. 190–209.

54. Renard, E. Implantable insulin delivery pumps. Minim. Invasive Ther. Allied Technol. 2004, 13, 328–335.

55. Bally, L.; Thabit, H.; Hovorka, R. Finding the right route for insulin delivery–an overview of implantable pump therapy. Expert Opin. Drug Deliv. 2017, 14, 1103–1111.

56. Sefton, M.V. Implantable pumps. Crit. Rev. Biomed. Eng. 1987, 14, 201–240.

57. King, B.R.; Goss, P.W.; Paterson, M.A.; Crock, P.A.; Anderson, D.G. Changes in altitude cause unintended insulin delivery from insulin pumps: Mechanisms and implications. Diabetes Care 2011, 34, 1932–1933.

Retrieved from https://encyclopedia.pub/entry/history/show/127503