Advanced Control in Vaccine Manufacturing

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Abstract: More than 300 COVID-19 vaccine candidates were under development as of April 26, 2022 [1]. Many COVID-19 vaccines are now available that reduce the probability of becoming infected and in reducing side effects for those individuals who become infected. Even after tens of billions of dollars of investment [2], the commercial vaccines in most countries do not prevent individuals from being infected. As such, variants will continue to develop that can reduce the effectiveness of existing vaccines, have increased infectivity, and lead to medical facilities becoming overwhelmed.

Many time-consuming engineering tasks are involved in going from the biology of creating a COVID-19 vaccine to the vaccination of billions of individuals needed to protect the world population. A major bottleneck to world-scale vaccination is the time required to develop a process to manufacture billions of doses within the existing supply chains and equipment while maintaining the highest levels of safety in the product. This talk describes ways in which process systems and control engineering is being applied for the purpose of reducing the current time required to manufacture large numbers of doses of vaccine. The primary emphasis is on mucosal vaccines, which provide much more robust immune response and stronger protection against viral infection than the non-mucosal vaccines such as sub-unit protein and mRNA vaccines currently commercially available for COVID-19 [3–6].

After a brief summary of the most promising COVID-19 vaccines and the bottlenecks in vaccine manufacturing in general, ways are described for using feedback control to shorten the timeline. The first set of technologies are applicable to all vaccine types and involve the use of fully automated modular manufacturing systems [7–9]. Control theory and algorithms are described for addressing the characteristics of these highly uncertain, nonlinear, hybrid, distributed parameter systems. The second set of technologies is specific to the main class of vaccines, live-attenuated viral vaccines, which use a weakened form of the virus. The close similarity of the vaccines to the natural infection creates a strong and long-lasting immune response. Such vaccines include influenza (flu), measles, mumps, rubella, rotavirus, smallpox, chickenpox, and yellow fever. In a case study, feedback control enables more than a factor of five increase in vaccine production.

References

1. COVID-19 vaccine tracker and landscape. World Health Organization. Accessed Feb. 5, 2022, https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
2. *Research and Development in the Pharmaceutical Industry*. Congressional Budget Office, page 11, April 2021.
3. Michael W. Russell, Zina Moldoveanu, Pearay L. Ogra, and Jiri Mestecky. Mucosal immunity in COVID-19: A neglected but critical aspect of SARS-CoV-2 infection. *Frontiers in Immunology*, 11, 611337, 2020.
4. Dennis Lapuente, Jana Fuchs, Jonas Willar, Ana Vieira Antão, Valentina Eberlein, Nadja Uhlig, Leila Issmail, Anna Schmidt, Friederike Oltmanns, Antonia Sophia Peter, Sandra Mueller-Schmucker, Pascal Irrgang, Kirsten Fraedrich, Andrea Cara, Markus Hoffmann, Stefan Pöhlmann, Armin Ensser, Cordula Pertl, Torsten Willert, Christian Thirion, Thomas Grunwald, Klaus Überla, and Matthias Tenbusch. Protective mucosal immunity against SARS-CoV-2 after heterologous systemic prime-mucosal boost immunization. *Nature Communications*, 12, 6871, 2021.

5. Ed C. Lavelle and Ross W. Ward, Mucosal vaccines – fortifying the frontiers, *Nature Reviews Immunology*, 22, 236–250, 2022.
6. Sam Afkhami, Michael R. D'Agostino, Ali Zhang, Hannah D. Stacey, Art Marzok, Alisha Kang, Ramandeep Singh, Jegarubee Bavananthasivam, Gluke Ye, Xiangqian Luo, Fuan Wang, Jann C. Ang, Anna Zganiacz, Uma Sankar, Natallia Kazhdan, Joshua F. E. Koenig, Allyssa Phelps, Steven F. Gameiro, Shangguo Tang, Manel Jordana, Yonghong Wan, Karen L. Mossman, Mangalakumari Jeyanathan, Amy Gillgrass, Maria Fe C. Medina, Fiona Smaill, Brian D. Lichty, Matthew S. Miller, and Zhou Xing. Respiratory mucosal delivery of next-generation COVID-19 vaccine provides robust protection against both ancestral and variant strains of SARS-CoV-2. *Cell*, 185(5), 896–915, 2022.
7. Amos E. Lu, Joel A. Paulson, Nicholas J. Mozdzierz, Alan Stockdale, Ashlee N. Ford Versypt, Kerry R. Love, J. Christopher Love, and Richard D. Braatz. Control systems technology in the advanced manufacturing of biologic drugs. P*roceedings of the IEEE Conference on Control Applications*, Sydney, Australia, 1505-1515, 2015.
8. M. S. Hong, K. A. Severson, M. Jiang, A. E. Lu, J. C. Love, and R. D. Braatz. Challenges and opportunities of biopharmaceutical manufacturing control. *Computers & Chemical Engineering*, 110, 106–114, 2018.
9. M. S. Hong, K. Kaur, N. Sawant, S. B. Joshi, D. B. Volkin, and R. D. Braatz. Crystallization of a nonreplicating rotavirus vaccine candidate. *Biotechnology & Bioengineering*, 118(4), 1750–1756, 2021.