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Editorial

The Matrix Reiterated

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This month, we would like to revisit the oft discussed subject of sample matrices and their role in the development of sensors. As you will know, the sample matrix is an issue close to the heart of our journal. Indeed, upon submission of any manuscript to *ACS Sensors*, authors will be reminded that "*papers should demonstrate the use of the sensor in complex samples appropriate to the application...*". Jean-Francois' 2020 editorial on the impact of the sample matrix on quantitative metrics, such as the limit of detection highlights many of the reasons why the sample matrix is so important when optimizing and benchmarking our sensors.[1] Here, we would like to reiterate some of Jean-Francois' opinions but also briefly discuss what can be done, both as individual researchers and a community of sensor developers, to navigate the tricky issue of sample matrices during sensor development.

To begin, it is instructive to define the term *sample matrix*. In its broadest sense, the sample matrix is everything present in a sample *except for* the analyte of interest.[2] It is the chemical and biological chaos surrounding the (often) vanishingly small amount of whatever you hope to detect. Many would liken this idea to the proverbial *needle in a haystack*, with the needle being the analyte and the haystack the sample matrix. In reality, the situation is even more problematic. At least a needle is made from a substantially different material to the hay in which it is buried, and the hay is not actively destroying the needle (or your tools) as you search for it. The same cannot be said for many of the analytes and sample matrices we deal with when developing sensors. Matrix components can adversely impact sensor performance in different ways (commonly referred to as matrix effects[3]), for example, by interfering with the binding between a sensing probe and the target,[4] degrading the target (or probe),[5] or disrupting a signaling cascade.[6] These examples are far from exhaustive.[1] So, if given the choice of finding a needle in a haystack or a single nucleotide mismatch in a sea of DNA and nucleases, you'd probably be wise to choose the needle.

Given this seemingly dire situation, it is no surprise that many researchers ignore the problem of the sample matrix altogether, instead opting to evaluate their sensors in simplified or "idealised" systems; often filtered buffers or solvents. Rather than searching for their needle in a haystack, they are instead trying to find it in a clean and tidy barn. While this approach can be an essential early step in the development of complete systems, researchers often fail to follow up on their work. A cynic might suggest that many sensors reported in the literature are simply incapable of operating effectively inside complex matrices and are thus never evaluated in this regard. An even greater cynic might suggest that researchers test their sensors in suitable matrices, find them lacking, and then fail to report the limitations of their work. This may be part of the trend to report "positive" results and a reluctance to report failures (an issue that is beyond the scope of this month's editorial). A more generous view would be that optimizing sensor performance in complex matrices is likely to be challenging and may require a great deal of time and funding. Many laboratories, particularly in resource-limited settings, lack both. Other reasons include difficulty obtaining/preparing suitable matrices, either due to material limitations or costs, or even a lack of knowledge of the ideal sample matrix for a particular analyte.

As an aside, it is worth pointing out that the suitability of sample matrices is not binary but rather a continuum. Some sample matrices are *more* suitable for a particular analyte, and some *less suitable*. For example, let us assume that we would like to develop a Point-of-Care (PoC) diagnostic platform designed to sense the RNA of a bloodborne virus. The ideal sample matrix would be whole blood containing (or spiked with) the virus, since this most closely resembles the sample type in the intended application. However, working with whole blood and viruses carries risks and requires specialized laboratories and equipment. A simplified approach would be to use the isolated genome of the virus spiked into commercial human serum, and simpler still would be to use a synthetic fragment of RNA containing the target spiked into a filtered buffer. Of these two options, the genome spiked into serum is clearly superior. So, while it is not always possible or practical to use the *ideal* sample matrix, there are still accessible ways to add complexity and move toward the ideal. Researchers should strive for the ideal but understand that adding even a small amount of complexity is better than adding none.

Whatever the reason for a collective reluctance to properly appreciate sample matrices, it is clearly an issue that needs to be addressed. So, what can be done to enable and incentivise researchers to go the extra mile? At the journal level, we believe it is an editor's responsibility to factor in the presence or absence of a "suitable" sample matrix when evaluating a new sensing technology, particularly if the technology is application-focused. Indeed, our current policy at ACS Sensors is that "*Application papers should demonstrate the use of the sensor in complex samples*", with other sensing journals having similar

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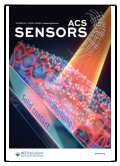

policies in place. Moving forward, broader interest journals should adopt these policies and ensure that they are clearly communicated to researchers.

At a community level, we could and should be far more ambitious. We should improve access to both sample matrices and "real samples". In its simplest form, this could mean openly sharing existing samples (within the confines of ethical practice) but should also involve creating community databases outlining suitable sample matrices for different types of sensors/analytes, including details on how to prepare or obtain these matrices. Funders could use their resources to support the establishment and upkeep of these collaborative networks and databases. In turn, this would allow us to better contrast and compare the utility of new sensing technologies in a wide range of environments. Ultimately, as a community, we must ask ourselves "*Do we want our sensing technologies to be genuinely useful for their intended applications?*" If the answer is yes, then as individual researchers we must make every effort to evaluate our sensors in *suitable* sample matrices, and as a community we should establish systems to enable others to do the same.

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Notes

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