Gender inequality infiltrates the in silico modeling world

Gender inequality has been the unspoken truth, rampant for centuries. Although a deep-rooted cultural mindset, the inequality has reverse-translated from society into the way we study and practice science, and more currently, into the computational modeling world.

Anirudh S. Chellappa, Madhulika Sahoo and Swagatika Sahoo

Over the decades, the progress of women's education and their presence in the workforce have been consistently low compared to their male counterparts. This is especially true when one looks at the participation of women in science, technology, engineering and mathematics (STEM) fields, including at a more advanced career level[1]. According to the United Nations Educational, Scientific and Cultural Organization (UNESCO) estimates, women represent less than 30% of the Research and Development workforce worldwide. Existing data revealed that women are globally under-represented in the STEM fields, especially at the PhD level and in research professions. Moreover, there is profound gender inequality in research and innovation[2], scientific medicine, medical knowledge, and practice, leading to extensive gender divisions in the society[3].

A recent report on *Bridging the Digital Gender Divide* suggested that girls had lower educational enrolment rates in STEM fields, which led to them being less equipped with digital tools and technical skills[4]. One of the factors is that women receive comparatively less financing for innovation and are often confronted with social and cultural barriers or 'glass ceilings', curbing their professional ambitions, especially so in science and technology. It was evident that the gender bias is more cultural since time immemorial. In many cultures, the gender roles are predefined: a woman should be good at soft skills, as they are considered to 'become' homemakers, taking care of the house, while men should excel at work for providing a living. In scientific research, it has been found that on an average females publish fewer research papers than males and are less likely to collaborate internationally[5]. Unfortunately, women are more susceptible to being squeezed out of science careers by structural social barriers. Reports by Science in Australia Gender Equity, the American Association of University Women, and the European Commission highlight that gender inequality is a function of systemic factors that are nowhere related to ability; instead, they are related to bias, organizational constraints, organizational culture, and differential effects of work and family demands[6,7]. An analysis of data from the Programme for International Student Assessment found that countries with high levels of gender equality have some of the largest gender gaps in secondary and tertiary education of STEM[8]. Furthermore, the under-representation of non-binary (or) genderqueer people in STEM has not escaped our notice. Given the paucity of information available on genderqueer people, especially those hailing from conservative and theocratic societies, it needs to be investigated in more detail.

Interestingly, this long-standing inequality has also infiltrated research practice. This is reflected in the way scientific data is acquired and analyzed. For instance, female rats were rarely used in experiments by neuroscientists, who reasoned that the cyclical oscillations in their reproductive hormones would impart confounding variability into their observations[9]. However, emerging evidence suggests that female rats are not more variable than male rats when studies of neuroscience-related traits are considered[10]. In a study in the United States, eight prescription medications were withdrawn from usage between 1997 and 2001 because it was discovered that they were more harmful to women than men. This had gone unnoticed because women were under-represented in the clinical trial[11,12]. First, there are the inherent differences in the prevalence of illnesses that influence the women to men ratio in clinical cohorts. For instance, in Alzheimer's disease women are disproportionately affected in comparison to men. On the other hand, in children meeting the criteria for autism spectrum disorder, the rates are higher in boys than girls[13]. Furthermore, in developing nations, factors like literacy rate, socio-economic status, health status and specific beliefs within communities also contribute to the drop-out rates and ascertainment biases in clinical cohorts[14].

This inequality in research practice can also be seen in the computational models that are developed by the research community. For instance, blood pressure regulation differs between women and men. Despite this, both receive the same antihypertensive therapy, which leads to fewer women achieving blood pressure control compared to men[15]. Kidneys are the key determinant of blood pressure[16]. While computational models of renal hemodynamics have been in development since the 1970s, practically most of them have been gender neutral. Recently, using the sex-specific parameters curated from published human studies, computational models of blood pressure regulation were built[17]. One of the key predictions was that when compared to angiotensin-converting enzyme inhibitors, the angiotensin receptor blockers reduce blood pressure more effectively in females, which was consistent with an independent clinical study. This was particularly attributed to the higher AT2R expression in afferent and efferent arterioles, and less excitable renal sympathetic nervous activity (RSNA) in women. While human models have clinical value, mechanistic understanding of the underlying pathophysiology necessitates the modeling and integration of rodent data. The blood pressure models were further updated using rodent data and the simulations suggested that the differential renal handling of sodium and RSNA in female rats may contribute to their observed lower salt sensitivity as compared with males[18].

This bias further extends into the reference knowledge bases that are constructed using such data. For instance, by integrating large volumes of data on the genome, biochemistry and physiological properties of humans, the metabolic reconstruction of a generic human cell,

that is, Recon3D, was built[19]. Recon3D was further constrained by anatomical, physiological, organ-resolved, multi-omics and microbiome data from humans to develop sex-specific whole-body metabolic models of a female (Harvetta) and a male (Harvey)[20]. While the models generated from Recon3D do provide a theoretical framework to interpret omics data, the sensitivity to predict biofluid-specific biomarkers for inborn errors of metabolism was significantly higher in the sex-specific models. Furthermore, the sex-specific models also predicted basal metabolic rates (BMRs) for Harvetta (1,344 kcal) and Harvey (1,455 kcal) that were consistent with the measured BMRs from literature. This presents a key advantage of using sex-specific models as opposed to generic ones. However, most of the computational models of human health and disease neglect the gender and sex dimension by collapsing the data into a point estimate.

Herein, we would like to provide some recommendations to avoid gender inequality in research practice. The cohorts should make efforts to mention the base prevalence of the illness across genders. The gender-wise base prevalence and drop-out rates should be considered 'before' sample recruitment and data generation. Appropriate statistical tests should be performed to test for trait differences across genders. While building computational models to represent normal physiology or diseases, efforts should be made to capture the effects of gender-specific parameters. Further, the computational modeling publications should mention the number of cases versus controls and number of male versus female subjects included in the original cohort and how many of those are incorporated into the model-building workflow. If few samples are dropped, appropriate explanations should be provided. While these recommendations are crucial in terms of the research methodology, they are merely a lip service, unless stringent systems are put in place to monitor and penalize gender bias in academic research practice or elsewhere. ❐

Anirudh S. Chellappa[1], Madhulika Sahoo[2] and Swagatika Sahoo[3,4] ✉

[1]Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, India. [2]Department of Anthropology, Kalahandi University, Odisha, India. [3]Office of Global Engagement, Indian Institute of Technology Madras, Chennai, India. [4]Centre for Integrative Biology and Systems medicine, Indian Institute of Technology Madras, Chennai, India.
✉*e-mail: swagatika05@gmail.com*

Published online: 20 June 2022
https://doi.org/10.1038/s43588-022-00268-3

References

1. *UNESCO Science Report: Towards 2030* (UNESCO, 2015); https://unesdoc.unesco.org/ark:/48223/pf0000235406
2. *She Figs 2015* (Publications Office of the EU, 2016); https://op.europa.eu/en/publication-detail/-/publication/f546dfed-41a9-11e6-af30-01aa75ed71a1
3. Verdonk, P., Benschop, Y. W. M., De Haes, H. C. J. M. & Lagro-Janssen, T. L. M. *Adv. Health Sci. Educ. Theory Pract.* **14**, 135–152 (2009).
4. *Bridging the Digital Gender Divide: Include, Upskill, Innovate* (OECD, 2018); https://www.voced.edu.au/content/ngv%3A81069
5. Shannon, G. et al. *Lancet* **393**, 560–569 (2019).
6. *Gender Equity in Higher Education* (SAGE, 2021); https://sciencegenderequity.org.au/about/gender-equity-in-higher-education/
7. *Solving the Equation: The Variables for Women's Success in Engineering and Computing* (AAUW, 2015); https://ww3.aauw.org/research/solving-the-equation/
8. Stoet, G. & Geary, D. C. *Psychol. Sci.* **29**, 581–593 (2018).
9. Fields, R. D. *Nature* **510**, 340 (2014).
10. Becker, J. B., Prendergast, B. J. & Liang, J. W. *Biol. Sex Differ.* https://doi.org/10.1186%2Fs13293-016-0087-5 (2016).
11. *Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women GAO-01-286R* (US Government Printing Office, 2001).
12. *Nature* **588**, 196 (2020).
13. Loomes, R., Hull, L. & Mandy, W. P. L. *J. Am. Acad. Child Adolesc. Psychiatry* **56**, 466–474 (2017).
14. Sindhu, K. N. et al. *BMC Med. Res. Methodol.* https://doi.org/10.1186%2Fs12874-019-0881-y (2019).
15. Gu, Q., Burt, V. L., Paulose-Ram, R. & Dillon, C. F. *Am. J. Hypertens.* **21**, 789–798 (2008).
16. Wang, L. et al. *Hypertension* **70**, 1219–1227 (2017).
17. Leete, J. & Layton, A. T. *Comput. Biol. Med.* **104**, 139 (2019).
18. Ahmed, S. & Layton, A. T. *Am. J. Physiol. Ren. Physiol.* **318**, F888 (2020).
19. Brunk, E. et al. *Nat. Biotechnol.* **36**, 272–281 (2018).
20. Thiele, I. et al. *Mol. Syst. Biol.* **16**, e8982 (2020).

Acknowledgements

A.S.C. is supported by Accelerator program for Discovery in Brain disorders using Stem cells (ADBS) (jointly funded by the Department of Biotechnology, Government of India, and the Pratiksha trust; grant BT/PR17316/MED/31/326/2015). S.S. was supported by DST-INSPIRE Faculty award, Department of Science and Technology, India (DST/INSPIRE/04/2015/000036).

Author contributions

A.S.C and S.S. contributed to the computational part, and M.S. was responsible for the social aspects of the study. All authors wrote the manuscript. S.S. designed and conceptualized the study.

Competing interests

The authors declare no competing interests.