EOSC-Life

Integration of the sex and gender dimension in life sciences research

Integration of the sex and gender dimension in life sciences research

The materials in this handbook were developed as part of the 3rd EOSC-Life Training Open Call. This resulted in the creation of the handbook, as well as a practical "Train the Trainer" session that took place in Barcelona at the Barcelona Supercomputing Center in June 2023. This handbook provides a comprehensive guide for trainers aiming to incorporate the sex and gender dimension into life sciences research. The handbook includes case studies and implementation guidelines to assist trainers in delivering effective training sessions. The **case studies** section covers various topics, exploring various didactic activities, presenting relevant literature, and providing key takeaways for the trainers. From the definitions of "sex" and "gender" and their implications in life sciences research to the complexities of moving beyond binary classifications, the concept of intersectionality, and the social impact of technology in the postgenomic era, the case studies highlight the importance of integrating a sex and gender-sensitive perspective in science, offering trainers practical examples to incorporate into their training sessions. This section explores the integration of the sex and gender dimensions into tools for bias mitigation. It delves into specific areas such as genetics, drug development, single cell multiomics, and artificial intelligence. The final section of the handbook presents implementation guidelines to assist trainers in enhancing communication skills, leading interactive sessions, and evaluating learning outcomes. It also provides a list of additional recommended readings for further topic exploration. Overall, this handbook equips trainers with the necessary tools, case studies, and **implementation guidelines** to effectively integrate the sex and gender dimensions in life sciences research. By promoting a more inclusive and comprehensive approach, trainers can foster greater understanding and contribute to advancements in the field.

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EOSC-Life

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DEFINITIONS OF "SEX" AND "GENDER"

MÓNICA CANO ABADÍA

BBMRI-ERIC

Introduction

Health experts frequently used the terms "sex" and "gender" interchangeably. Nonetheless, academics and policymakers that support the inclusion of sex and/or gender in healthcare fields, encourage people to draw distinctions between the two.

In the 1980s, interest in sex and gender effects on biology and health began to grow. By the 1990s and the beginning of the 2000s, numerous research funding organizations, authorities, and journal editors were urging and requiring academics to take sex and gender into account in their work.

Definition of gender

See this definition of "gender" by the Canadian Institutes of Health Research.

Gender refers to the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender identity is not confined to a binary (girl/woman, boy/man) nor is it static; it exists along a continuum and can change over time. There is considerable diversity in how individuals and groups understand, experience and express gender through the roles they take on, the expectations placed on them, relations with others and the complex ways that gender is institutionalised in society (CIHR Institute of Gender and Health, 2023).

Gender can be understood as those aspects of social organisation that establish roles, expectations, relationships, behaviours, aesthetics, and activities that are considered proper in relation to temporal and cultural concepts of sex. The expression of one's gender through clothing, grooming, mannerisms, and speech; adherence to cultural norms of femininities and masculinities; and the adoption of characteristics like toughness, nurturing, and emotionality that are typically associated with one's gender or sex category are all included at the individual level.

The way that relationships and interactions are shaped by (gendered) norms, (gendered) rules, and (gendered) practices are all influenced by gender. Gender underpins social roles in the home, workplace, political, religious, and other arenas. Although the masculine/feminine dichotomy is frequently used to understand gender, there is actually a great deal of cultural and historical variation in the ways that gender is built, constructed, and enacted. Gender is thus multidimensional and complex and may include women, men, and non-binary people.

Further information here.

Definition of sex

See this definition of "sex" by the Canadian Institutes of Health Research.

Sex refers to a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorised as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed (CIHR Institute of Gender and Health, 2023).

Further information here.

Why do these definitions matter?

The American Medical Association updated its policies in 2018 to affirm the medical spectrum of sex and gender by stating that "sex and gender are more complex than previously assumed. (…) It is essential to acknowledge that an individual's gender identity may not align with the sex assigned to them at birth. A narrow limit on the definition of sex would have public health consequences for the transgender population and individuals born with differences in sexual differentiation, also known as intersex traits" (American Medical Association, 2018).

In late 2020, the European Commission announced that its research-grant recipients would need to incorporate analyses of sex and gender in their study design. This could include disaggregating data by sex when examining cells, or considering how a technology might perpetuate gender stereotypes (Directorate-General for Research and Innovation, European Commission, 2020).

One of the leading medical journals, The Lancet, updated their author guidelines (The Lancet, 2023), encouraging the enrolment of women and ethnic groups into clinical trials and to analyse the data accordingly, considering influences and associations of sex and gender.

Nature Magazine has updated guidance on reporting on sex and gender in research studies. The changes were announced in a Nature editorial ("Raising the Bar on Sex and Gender Reporting in Research," 2022); four journals will be testing a more stringent application of the guidance.
Nonetheless, researchers should be careful when using these categories. The actual distribution of data rarely supports a neat division of males and females into distinct groups. Indeed sex- and gender-related differences "commonly takes the form of average differences between females and males but with considerable overlap in distributions" (Pape, 2021). In many instances, the sex or gender category of an individual is not a strong predictor of that individual's behaviour, expression of a trait, or response to a treatment. See this case study to understand the problems that stem from overemphasising gender differences.

Additionally, given that both sex and gender are highly complex, any classification of them is going to be limited. See this ontology which showcases the multiple classifications that can be done within gender, sex, and sexual orientation: Complexity of gender: GSSO - the Gender, Sex, and Sexual Orientation ontology.

Selected resources

- Kim, N., & Schiebinger, L. (2022). Why Is Sex/Gender-Specific Medicine Needed? In N. Kim (Ed.), Sex/Gender-Specific Medicine in the Gastrointestinal Diseases (pp. 3-10). Singapore: Springer Nature Singapore.

This paper shows how sex and gender interact to influence health outcomes. Sex/gender-specific medicine refers to the medical study of differences between women, men, and non-binary people who frequently present with different symptoms of a particular disease and may respond differently to treatment. These differences can be caused by the effects of sex hormones or genetic predispositions on disease mechanisms (i.e., pathophysiology) and by sociocultural factors related to gender, socioeconomic status, or educational background. Studies must integrate both sex and gender analysis into the research design and analyse how sex and gender interact.

- Nielsen, M. W., Stefanick, M. L., Peragine, D., Neilands, T. B., Ioannidis, J. P. A., Pilote, L., . . . Schiebinger, L. (2021). Gender-related variables for health research. Biology of Sex Differences, 12(1), 23. doi:10.1186/s13293-021-00366-3.

This questionnaire is designed to shed light on how specific gender-related behaviours and attitudes contribute to health and disease processes, irrespective of-or in addition to-biological sex and self-reported gender identity. A new instrument which contributes to developing more comprehensive and precise survey-based measures of gender in relation to health.

- Fausto-Sterling, A. (2012). Sex/gender: biology in a social world. New York: Routledge New York.

This book presents a new way to think about how biological differences can be produced over time in response to different environmental and social experiences. The author provides an introduction to the biochemistry, neurobiology, and social construction of gender.

Proposed didactic activities

- Self-reflection on the two questions below. Then, sharing in pairs or small groups; then sharing in the plenary.

    - What (if any) "background assumptions" about sex and gender shape or are embedded in the concepts and theories in your field? These may not be explicit.

    - What issues related to sex and gender are not being addressed, or are misunderstood or misrepresented, as a result of how concepts and theories are framed in the field? For example, the concept of the "out-of-position driver" rules out certain people as part of the population that engineers design for (see the Gendered Innovations case study: Inclusive Crash Test Dummies).

- In groups, explore this ontology: GSSO - the Gender, Sex, and Sexual Orientation ontology
  - Check the category of gender.
  - Did you know that all these categories existed?
  - Find information online on the categories that you do not know.
- Discussion in groups: See the definition of "gender" and "sex" by the Canadian Institutes of Health Research. See also Figure 1 with provisional definitions of sex and gender in this article: Ritz, S. A., & Greaves, L. (2022). Transcending the Male-Female Binary in Biomedical Research: Constellations, Heterogeneity, and Mechanism When Considering Sex and Gender. Int J Environ Res Public Health, 19(7). doi:10.3390/ijerph19074083:
  - Discuss the differences between the concepts of "sex" and "gender".
  - Have you ever seen these differences in your area of expertise?
- Discussion in groups: See Figure 1 "Analyzing sex throughout the research process" in this paper: Schiebinger, L. (2022). Sex, gender, and intersectional puzzles in health and biomedicine research. Med, 3(5), 284-287. https://doi.org/10.1016/j.medj.2022.04.003
  - Discuss:
    - Were you aware of all the ways in which sex can play a role in different phases of the research process?
    - Have you ever considered conducting a literature review on sex and gender issues in the field prior to performing research?
    - Do you think it would be possible to do research this way in your institution?
    - Can you identify people in your institution who would support conducting research this way?

Takeaways

- Usually, sex and gender are used interchangeably in research. Nonetheless, conceptual differences must be drawn.
- Both sex and gender are multifaceted and complex; therefore, they resist binary classifications and their complexity should be reflected in life sciences research.
- A situated approach will help assess the relevance of different variables for distinct case studies.

BEYOND BINARY CLASSIFICATIONS

MÓNICA CANO ABADÍA

BBMRI-ERIC

Introduction

The sex binary refers to the traditional understanding of sex as a strict division into two distinct categories: male and female. This binary view is based primarily on biological characteristics such as reproductive organs, chromosomes, and hormones. In this framework, individuals are typically assigned a sex at birth based on physical attributes, and this assignment is considered to be either male or female.

According to the sex binary perspective, males possess certain characteristics typically associated with masculinity, such as a penis, XY chromosomes, and higher levels of testosterone, while females possess characteristics associated with femininity, such as a vagina, XX chromosomes, and higher levels of oestrogen.

However, it is crucial to acknowledge that the sex binary oversimplifies the intricate biological and physiological variations observed in human beings. The concept of biological sex is not always straightforward, as there exists a possibility of intersex individuals who possess a combination of both male and female anatomical features or exhibit chromosomal variations. The reliance on male-female binary conceptualisations of sex disregards the crucial realities of trans individuals and those with intersex variations and differences in sexual development, who constitute a significant proportion of the population.

Furthermore, the sex binary fails to accommodate the vast spectrum of gender identities that individuals may identify with, which may deviate from the sex assigned at birth. Gender identity is an intensely personal and subjective experience that may not align with the traditional male/female categorisation.

Instead of perceiving sex as a strict division into two distinct categories of male and female, it might be more precise to view it as a collection or arrangement of sex-related characteristics. We can compare this to constellations in the night sky, which are groupings of stars that humans have identified as significant and recognisable. Just as no individual star solely defines a constellation or is defined by its place within it, no single trait can definitively determine sex, and no particular trait exclusively belongs to one sex.

The category of sex has had its own history and even within our Western culture we have had different understandings of sex. In certain ancient civilisations, sex was often viewed through a dualistic lens, associating it with opposing forces like male and female, active and passive, or light and dark. However, these conceptualisations were not solely based on biological characteristics but also incorporated cultural, mythological, and religious elements.

During the 18th and 19th centuries, with the rise of modern science and medicine, there was an increasing emphasis on biological determinism, as the recommended book by Thomas Laqueur shows (see selected resources). Scholars sought to classify and categorise individuals into discrete sex categories primarily based on visible physical attributes such as genitalia. This binary framework became widely accepted and formed the foundation of the contemporary understanding of sex.

With chromosomal discoveries in the early 20th century, advancements in genetics led to the discovery of chromosomes and their role in determining sex. In 1959, the discovery of the XX/XY chromosomal sex determination system further solidified the binary view of sex. This understanding reinforced the belief that sex is solely determined by one's chromosomal makeup, overlooking other biological and intersex variations.

The late 20th century saw a growing recognition of intersex individuals who possess atypical combinations of physical sex characteristics. Intersexuality challenges the binary understanding of sex, highlighting the existence of variations that do not fit neatly into male or female categories. This recognition has prompted discussions on the limitations of the sex binary and the need for a more inclusive understanding of sex.

In parallel to discussions about biological sex, the distinction between sex and gender gained prominence. While sex refers to biological characteristics, gender encompasses the roles, behaviours, and identities associated with being male or female in a given society. The understanding of gender as a social construct separate from sex has allowed for more nuanced discussions about the diversity of gender identities beyond the traditional male/female binary.

In recent years, there has been a significant shift towards recognising and respecting a broader spectrum of sex and gender identities. This includes acknowledging the existence of non-binary, genderqueer, and gender non-conforming individuals, who do not exclusively identify as male or female.

Additionally, there are numerous examples of cultures and societies that have recognised and incorporated non-binary understandings of sex and gender. Here are a few notable examples:

- Two-Spirit (Various Indigenous Cultures): Many Indigenous cultures in North America, such as the Native American tribes, have long recognised the existence of Two-Spirit people. Two-Spirit is an umbrella term that encompasses diverse gender identities and expressions that differ from the male/female binary. Two-Spirit individuals often embody both masculine and feminine qualities and play significant cultural and ceremonial roles within their communities.

- Hijra (South Asia): In South Asian societies, particularly in India, Pakistan, and Bangladesh, the Hijra community has a long history and cultural recognition. Hijras are assigned male at birth but identify and live as a distinct third gender. They often form their own communities and have unique social roles, such as performing at ceremonies and providing blessings.

- Fa'afafine (Samoa and Polynesia): Fa'afafine is a term used in Samoan and other Polynesian cultures to describe individuals who are assigned male at birth but take on female gender roles and identities. They are socially accepted as a distinct gender category and often fulfil important familial and community roles.

- Sworn Virgins (Balkan Region): In certain regions of the Balkans, there is a cultural practice known as Sworn Virgins. These are assigned female individuals who choose to live as men, adopting male clothing, roles, and responsibilities. This practice typically occurs in patriarchal communities and is often motivated by factors such as inheritance rights or the desire to maintain familial honour.

- Guevedoche (Dominican Republic): The term guevedoche refers to individuals born with atypical genitalia in the Dominican Republic. These individuals are assigned female at birth but develop male secondary sexual characteristics during puberty due to a condition called 5-alpha-reductase deficiency. This example highlights the recognition of biological variations beyond the male/female binary and challenges the notion of strictly binary sex classification.

These are just a few examples, and it is important to note that diverse understandings of sex and gender exist across cultures. Each culture has their own unique ways of recognising and categorising individuals outside of the male/female binary, highlighting the rich diversity of human experiences and identities.

Why is this important?

Integrating a non-binary understanding of sex and gender is important for the life sciences for several reasons:

- Accurate representation of human diversity: Recognising and incorporating non-binary understandings of sex and gender allows for a more comprehensive and accurate representation of the diversity of human experiences. The life sciences aim to study and understand human biology, and by acknowledging the existence of non-binary identities, researchers can avoid oversimplification and exclusion of important populations.

- Addressing health disparities: Failure to consider non-binary individuals in research and healthcare can lead to significant health disparities. Non-binary individuals may have unique health needs, experiences, and vulnerabilities that differ from cisgender individuals. By integrating a non-binary understanding of sex and gender, the life sciences can ensure that research, medical treatments, and healthcare policies are inclusive and responsive to the specific needs of non-binary individuals.

- Enhancing scientific rigour: Embracing a non-binary understanding of sex and gender enhances scientific rigour by challenging assumptions and biases. By acknowledging the complexity of sex and gender, researchers can develop more nuanced research designs, methodologies, and data analysis strategies that account for the diverse range of biological and gender identities. This can lead to more accurate and reliable scientific findings.

- Promoting ethical research practices: Recognising and respecting non-binary identities in the life sciences promotes ethical research practices. It ensures that research participants are treated with dignity, respect, and autonomy, and that their identities are acknowledged and validated. It also encourages the inclusion of non-binary individuals in research studies, allowing for a more representative sample and avoiding exclusionary practices that perpetuate marginalisation.

- Advancing Social Progress: By embracing a non-binary understanding of sex and gender, the life sciences can contribute to social progress and inclusivity. It promotes a society that recognises and affirms the identities and experiences of all individuals, regardless of their gender. This has broader implications beyond the scientific realm, fostering a more inclusive and equitable society for all.

Selected resources

- DuBois, L. Z., & Shattuck-Heidorn, H. (2021). Challenging the binary: Gender/sex and the bio-logics of normalcy. Am J Hum Biol, 33(5), e23623. doi:10.1002/ajhb.23623

This paper discusses biological variation associated with gender/sex and propose ways forward to ensure we are engaging with gender/sex diversity. It concludes with guidelines and methodological suggestions for how to engage gender/sex and gender identity in research.

- Fausto-Sterling, A. (2000). Sexing the body: gender politics and the construction of sexuality (1st ed ed.). New York, NY: Basic Books New York, NY.

Drawing on astonishing real-life cases and a probing analysis of centuries of scientific research, feminist biologist Fausto-Sterling demonstrates how scientists have historically politicised the body. She breaks down three key dualisms - sex/gender, nature/nurture, and real/constructed - and asserts that individuals born as mixtures of male and female exist and should not be forced to compromise their differences to fit a flawed societal definition of normality.

- Fausto-Sterling, A. (2018, 2018-10-25). Why Sex Is Not Binary. The New York Times. Retrieved from https://www.researchgate.net/publication/338234318_Why_Sex_Is_Not_Binary_591.

In this article, Fausto-Sterling shows how the complexity of sex is not only cultural but also biological.

- Johnson, E. (2005). The ghost of anatomies past Simulating the one-sex body in modern medical training. Feminist Theory, 6(2), 141-159. doi:10.1177/1464700105053691

This article shows how the widely held modernist understanding of sex and gender as binary categories is actually masking local practices which allow varied sex and gender paradigms to coexist in simulator use.

- Joel, D. (2021). Beyond the binary: Rethinking sex and the brain. Neurosci Biobehav Rev, 122, 165-175. doi:10.1016/j.neubiorev.2020.11.018

The paper reviews the relations between sex and the brain in light of the binary conceptualisation of these relations and the challenges posed to it by the 'mosaic' hypothesis. Mosaic brains reside in a multi-dimensional space that cannot meaningfully be reduced to a male-female continuum or to a binary variable. This framework may also apply to sex-related variables and has implications for research.

- Laqueur, T. (1992). Making Sex. Body and Gender from the Greeks to Freud: Harvard University Press.

This book tells the astonishing story of sex in the West from ancient to modern times in a precise account of developments in reproductive anatomy and physiology.

- Montañez, A. (2017, August 29). Visualizing sex as a spectrum. Retrieved from https://blogs.scientificamerican.com/sa-visual/visualizing-sex-as-a-spectrum/

This infographic reveals the startling complexity of sex determination.

- BBMRI ERIC. (2022, December 14). ELSI Dialogues - Visualizing the Complexity of Sex Determination [Video file]. Retrieved from https://www.youtube.com/watch?v=xsttPikUnwo

In this webinar, Amanda Montañez explains the process of how the graphic Beyond XX and XY was developed, what she learned, and how this project fits into her work as a graphics editor.

- Ritz, S. A., & Greaves, L. (2022). Transcending the Male-Female Binary in Biomedical Research: Constellations, Heterogeneity, and Mechanism When Considering Sex and Gender. Int J Environ Res Public Health, 19(7). doi:10.3390/ijerph19074083

This article highlights how practices of data visualisation, statistical analysis, and rhetoric can be valuable tools in expanding the operationalisation of sex and gender biomedical science and reducing reliance on a male–female binary approach.

- Tannenbaum, C., Ellis, R. P., Eyssel, F., Zou, J., & Schiebinger, L. (2019). Sex and gender analysis improves science and engineering. Nature, 575(7781), 137-146. doi:10.1038/s41586-019-1657-6

This paper provides a roadmap for sex and gender analysis across scientific disciplines and calls on researchers, funding agencies, peer-reviewed journals, and universities to coordinate efforts to implement robust methods of sex and gender analysis.

Proposed didactic activities

- Discuss Amanda Montañez's infographic in groups of 2-4 people. Then, share your thoughts with the plenary. Source: Beyond XX and XY
    - Guided discussion:
        - Did you know that sex is so diverse?
        - How do you think the diversity of sex can be applied to your field of expertise?

Takeaways

- The sex binary categorises individuals into male and female based on biological characteristics such as reproductive organs, chromosomes, and hormones.
- The sex binary oversimplifies the complexity of human biology, as intersex individuals can possess a combination of male and female anatomical features or chromosomal variations.
- The sex binary does not account for the wide spectrum of gender identities that individuals may identify with, which can differ from the sex assigned at birth.
- Cultures around the world have recognised and incorporated non-binary understandings of sex and gender, such as Two-Spirit in Indigenous cultures, Hijra in South Asia, Fa'afafine in Samoa and Polynesia, and Sworn Virgins in the Balkans.

INTERACTIONS BETWEEN SEX AND GENDER

MÓNICA CANO ABADÍA

BBMRI-ERIC

Introduction

Although the concepts of sex and gender can and should be analytically differentiated, in practice, sex and gender are in a dynamic dialogue with one another and interact in ways that highlight and generate the realities of living in sexed and gendered bodies. Such interactions can often make it difficult to draw a clear line between them.

To demonstrate this, feminist biologist Anne Fausto-Sterling used the concept of bone density (Fausto-Sterling, 2005). It can be easy to blame sex-related variables for differences in bone density between men and women since bones appear to be unmistakably biological and are influenced by gonadal hormones. Bone density is affected by a variety of gender-specific characteristics as well, though. Gendered job duties and social conventions can influence the type, degree, and frequency of weight-bearing activities a person engages in. A wide range of gender-related factors, such as gendered clothing norms and religious veiling practices, health-seeking behaviours like the use of sunscreen, and participation in outdoor jobs and recreation, influence sun exposure. In a similar vein, exposure to sunlight stimulates vitamin D synthesis, which is crucial for maintaining bone homeostasis.

Further information here.

Selected resources

- Stefanick, M. L., & Schiebinger, L. (2020). Analysing how sex and gender interact. Lancet, 396(10262), 1553-1554. doi:10.1016/s0140-6736(20)32346-1

This article focuses on how knowledge is produced in a gendered way. The authors claim that it is time to integrate how sex and gender interact into basic and applied research.

- Krieger, N. (2003). Genders, sexes, and health: what are the connections—and why does it matter? International Journal of Epidemiology, 32(4), 652-657. doi:10.1093/ije/dyg156

This paper provides examples of how not only can gender relations influence expression—and interpretation—of biological traits, but also sex-linked biological characteristics can, in some cases, contribute to or amplify gender differentials in health.

Proposed didactic activities

- Discuss this paragraph:

  A patient has sex characteristics that affect how they feel pain, but the patient is also influenced by gender norms in the culture they live in, and this may influence how that patient feels and expresses pain. Gender norms, for example, may influence a person's willingness to report pain. In many cultures, men are expected to be strong and resolute, which means that men may be less willing to express pain than women. This varies by ethnicity and other social factors. Physician gender stereotypes may also influence their choice of treatments for men and women. Clinicians often perceive women's pain to be psychological, and women may receive more non-specific diagnoses, wait longer for treatment, and receive more antidepressants and fewer painkillers than men. Consequently, the treatment a patient receives depends in part on the patient's gender and on the physician's gender assumptions. To my knowledge, this has not been studied in nonbinary patients. (Source: Schiebinger, L. (2022). Sex, gender, and intersectional puzzles in health and biomedicine research. Med, 3(5), 284-287. https://doi.org/10.1016/j.medj.2022.04.003).

Takeaways

- Sex and gender interact with each other and with people's environment.
- Sex and gender are not static categories.

INTEGRATION OF SEX - AND GENDER - SENSITIVE PERSPECTIVE IN LIFE SCIENCES RESEARCH

MÓNICA CANO ABADÍA

BBMRI-ERIC

Introduction

It is important to integrate both gender and sex in health and life sciences research, understanding sex as a biological variable and gender as a social and structural variable.

When it comes to sex, up until recent decades, the vast majority of clinical studies included only or mostly male patients. Additionally, nearly solely male cells or male animals were used in most preclinical studies using animal and cell models, which were used to advance our understanding of human biology and disease. Despite this constrained methodology, it was frequently assumed—and occasionally still is—that the study findings and medical treatments derived from this knowledge applied to the entire population.

Our understanding of the life sciences is incomplete because of this systematic underrepresentation of women, transgender, and intersex people. The lack of adequate evidence continues to have an impact on patient care, which might result in delayed or incorrect diagnoses among female patients. Additionally, drugs are less effective and more dangerous for female patients as a result of the underrepresentation of female patients in clinical research and the absence of sex-based data analysis.

When it comes to gender, it plays a significant role in understanding how each person's physical and mental health and well-being are affected in a variety of ways. For instance, it has been demonstrated that a society's gender disparities restrict women's and girls' access to health care and, at the same time, gender norms and stereotypes around masculinity limit the way in which boys and men seek health treatments.

It is important to have a situated approach to understanding how to introduce a sex-and gender-sensitive perspective in order not to perpetuate bias and stereotypes. Situatedness refers here to a perspective that considers that meaning depends on the specifics of particular sociohistorical, geographical, and cultural contexts. Different contexts, research designs, scientific applications, etc., will grant different needs in integrating sex and gender, which need to be assessed on a case-by-case basis.

For example: the project Gendered Innovations talks about the case study of knee replacements which used gender as a category to produce (and market) different knee replacements for men and women, in which gender seems to be here a proxy for height and weight, which are categories that are more relevant to know which knee replacement might be needed by a patient. See the complete case study here: De-Gendering the Knee: Overemphasizing Sex Differences as a Problem | Gendered Innovations. (2023). Retrieved from https://genderedinnovations.stanford.edu/case-studies/knee.html

In sum, the study of how sex and gender influence health and disease is central to improving health, lengthening life, and reducing illness for all people.

Selected resources

- What are Sex & Gender? And why do they matter in health research? Sex & Gender | Office of Research on Women's Health. (2023). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

This webpage highlights the importance of integrating both sex and gender in health research, understanding sex as a biological variable and gender as a social and structural variable.

- Vader, S. S., Lewis, S. M., Verdonk, P., Verschuren, W. M. M., & Picavet, H. S. J. (2023). Masculine gender affects sex differences in the prevalence of chronic health problems - The Doetinchem Cohort Study. Prev Med Rep, 33, 102202. doi:10.1016/j.pmedr.2023.102202

The study examines the influence of masculinity (based on traditional masculine aspects) on sex differences in chronic health problems. Men had higher masculinity scores than women. Higher masculinity scores were associated with lower prevalence of chronic health problems in both sexes.

Gender adjustment revealed greater sex differences in diabetes, CHD, and CVA, while smaller sex differences were found in arthritis, chronic pain, and migraine. The findings highlight the relevance of gender in understanding sex differences in health, indicating a significant gender component in prevalent chronic health problems.

- Wood, H, and Harjes. U (eds.). Women's health. (2021, March 8). Retrieved on 2023, June 15 from https://www.nature.com/collections/hhegjbfjdi

This regularly updated collection of articles published in the Nature Reviews journals provides in-depth discussions of recent research and medical advances in fields covering women's health in the broadest sense.

- Gender Equality in Academia and Research - GEAR tool. Integration of the sex/gender dimension into research and teaching content. (2023).

This toolkit hosts a collection of resources to integrate the gender dimension in research and teaching content.

- Understanding Influences of Sex and Gender in Health and Disease. Sex and Gender in Health and Disease | Office of Research on Women's Health. (2023).

This infographic illustrates the influences of sex and gender in health and disease.

- GSSO - the Gender, Sex, and Sexual Orientation ontology. GSSO - Ontology Lookup Service. (2023).

This ontology shows a thorough classification of different categories of sex and gender.

- How to integrate sex and gender into research. CIHR. (2018).

These guidelines, tools and resources help researchers and reviewers better account for sex and gender in health research.

Proposed didactic activities

- Vader, S. S., Lewis, S. M., Verdonk, P., Verschuren, W. M. M., & Picavet, H. S. J. (2023). Masculine gender affects sex differences in the prevalence of chronic health problems - The Doetinchem Cohort Study. Prev Med Rep, 33, 102202. doi:10.1016/j.pmedr.2023.102202

- Groups of 3-4 people: Read this case study and discuss:

  De-Gendering the Knee: Overemphasizing Sex Differences as a Problem | Gendered Innovations. (2023). Retrieved from https://genderedinnovations.stanford.edu/case-studies/knee.html

  Questions:

  - Do you know any other examples of overemphasis of gender and sex categories?
    - How does overemphasising sex differences pose a problem in this case study?
    - How would you approach this problem?

Takeaways

- It is important to integrate a sex- and gender-sensitive perspective in the life sciences in order to mitigate potential biases and ensure that scientific knowledge is being produced in an accurate, precise, and responsible manner.

- For the integration of sex- and gender-sensitive perspectives in the life sciences it is crucial to understand sex as a biological variable and gender as a social and structural variable.

- A broad (and scientifically accurate) understanding of sex and gender, which includes more than the traditional binary categorisation, is necessary to ensure our understanding of the life sciences is striving for accuracy.

SEX AND GENDER DIMENSION IN THE GENETICS OF SEX DETERMINATION

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Introduction

The relationship between sex, genetics, and brain development is extremely intricate and complicated. Throughout the years, studies have revealed epigenetic patterns in the brains of animals, such as rats, indicating sex-specific expression patterns in cognitive and endocrine functions. There is a critical period of sexual differentiation playing a vital role in shaping the male/female brains and the specific regions controlling these differences (McCarthy, Herold, & Stockman, 2018).

Furthermore, there's a strong interplay between sex chromosomes, hormonal programming, and androgens during embryogenesis. They strongly influence genetic expression and developmental programming. The sex differences occurring from these variations affect cognitive functions, neurodevelopment and even the appearance of neurological and psychiatric disorders (Chung & Auger, 2013; Phillips et al., 2019).

Finally, the need to characterise the precise genetics of sex determination is highlighted due to the wide variety of variations leading to diverse and unique sexual-genetic profiles (Laino et al., 2014; Ristori et al., 2020; Bashamboo & McElreavey, 2016). Understanding the interplay between genetics, sex determination, and brain development is crucial for unveiling and comprehending the complexities of sex and gender dimensions in human biology.

Selected resources

- It is important to integrate a sex- and gender-sensitive perspective in the life sciences in order to mitigate potential biases and ensure that scientific knowledge is being produced in an accurate, precise, and responsible manner.

The paper discusses the differences between male and female brains and how they are formed during the critical period of sexual differentiation.

One example of a well-known sex difference in the mammalian brain is the sexually dimorphic nucleus (SDN) of the preoptic area (POA) in rats, which is larger in males than in females. Females have a longer sensitive period than males, which allows for the experimental recapitulation of masculinisation by treating female pups after they have been born. However, blocking masculinisation as it occurs naturally in males is more difficult.

- Chung, W. C., & Auger, A. P. (2013). Gender differences in neurodevelopment and epigenetics. Pflugers Arch, 465(5), 573-584. doi:10.1007/s00424-013-1258-4

This paper presents a literature review highlighting the importance of sex differences in the development and structuring of the brain.

As mentioned in the introduction, these differences can affect cognitive functions and the incidence of neurological and psychiatric diseases.

The main focus is on the gonadal steroid hormone, testosterone, and its metabolites affecting downstream signalling cascades and epigenetic events to reach gender-dependent differentiation.

- Phillips, O. R., Onopa, A. K., Hsu, V., Ollila, H. M., Hillary, R. P., Hallmayer, J., . . . Singh, M. K. (2019). Beyond a Binary Classification of Sex: An Examination of Brain Sex Differentiation, Psychopathology, and Genotype. J Am Acad Child Adolesc Psychiatry, 58(8), 787-798. doi:10.1016/j.jaac.2018.09.425.

The paper presents new evidence supporting how sex differentiation can be followed and monitored in order to understand the observed sex differences in psychopathology. Continuous variables measuring can be performed with brain imaging data and other parameters influencing the development of sex biased psychopathologies.

It concludes by highlighting the need to move away from binary understandings of sex differences and view the sex of the human brain as a spectrum.

- Laino, L., Majore, S., Preziosi, N., Grammatico, B., De Bernardo, C., Scommegna, S., . . . Grammatico, P. (2014). Disorders of sex development: a genetic study of patients in a multidisciplinary clinic. Endocr Connect, 3(4), 180-192. doi:10.1530/ec-14-0085.

Establishing a precise aetiology is crucial to categorise sex and assign it more accurately. This paper samples 88 individuals and presents the genetic characteristics and alterations that can occur in the different disorders of sex development (DSD) for a better nomenclature and diagnosis.

- Ristori, J., Cocchetti, C., Romani, A., Mazzoli, F., Vignozzi, L., Maggi, M., & Fisher, A. D. (2020). Brain Sex Differences Related to Gender Identity Development: Genes or Hormones? Int J Mol Sci, 21(6). doi:10.3390/ijms21062123.

This article reviews relevant studies on sexual development with a focus on hormones and gender identity. Different studies demonstrate how gender identity also affects sex, as the brain's sexually dimorphic structures in many instances better align with their individual gender rather than their assigned sex. This has been further supported by transgender studies.

Although sex affects human behaviour, there are no candidate genes at the moment creating a deeper need to understand the relationship between sex, gender, genetics, hormones and how they affect psychosexual development.

- Bashamboo, A., & McElreavey, K. (2016). Mechanism of Sex Determination in Humans: Insights from Disorders of Sex Development. Sex Dev, 10(5-6), 313-325. doi:10.1159/000452637.

The paper discusses the subtle differences in the genetics of the sex-determining system between humans and mice of human DSD found in their study.

They suggest that the plasticity of the sex-determining pathway may be greater than previously thought. The paper lists and provides information on the considerable number of new genes involved in human sex determination that when mutated cause non-syndromic DSD e.g., NR5A1, MAP3K1, GATA4, FOG2, SOX9, SOX3, OVARYSOX10.

- Montañez, A. (2017, August 29). Visualizing sex as a spectrum. Retrieved from https://blogs.scientificamerican.com/sa-visual/visualizing-sex-as-a-spectrum/.

Up to this date, humans, and specially the medical field, have considered sex as a rigid binary category. Sexually dimorphic individuals and those who don't fit into male/female dichotomies are generally excluded from studies and conclusions. It is important to have a broad and flexible categorisation based on sex and gender in order to include intersex individuals, transgender individuals, and non-binary individuals in studies as a way of offering more effective and personalised medicine.

This infographic presents a great visual representation and exploration of complexity in a graphic that emphasises the importance of recognising the diverse manifestations and pathways of development in DSDs.

- Menger, Y., Bettscheider, M., Murgatroyd, C., & Spengler, D. (2010). Sex differences in brain epigenetics. Epigenomics, 2(6), 807-821. doi:10.2217/epi.10.60

The paper highlights the differences in the epigenetic patterns in rats' brains. The epigenetic regulators demonstrate sex and time specific expression in brain regions and involvement not only in sexual determination, but also endocrine and cognitive differences and even response to brain injury.

- Holterhus, P. M., Bebermeier, J. H., Werner, R., Demeter, J., Richter-Unruh, A., Cario, G., . . . Hiort, O. (2009). Disorders of sex development expose transcriptional autonomy of genetic sex and androgen-programmed hormonal sex in human blood leukocytes. BMC Genomics, 10, 292. doi:10.1186/1471-2164-10-292.

The paper analyses different components of gender during development and embryonic programming with a focus on DSD. However, this paper considers gender as the expression of the sexual characteristics. Differences in expression arise during embryogenesis and are caused by a combination of sex chromosomes, hormonal programming, and the androgen milieu.

Proposed didactic activities

The activity will use the information from:

The Genetics of Sex Determination: Rethinking Concepts and Theories and Visualizing sex as a spectrum.

Considering the following genes/molecules involved in sex determination:

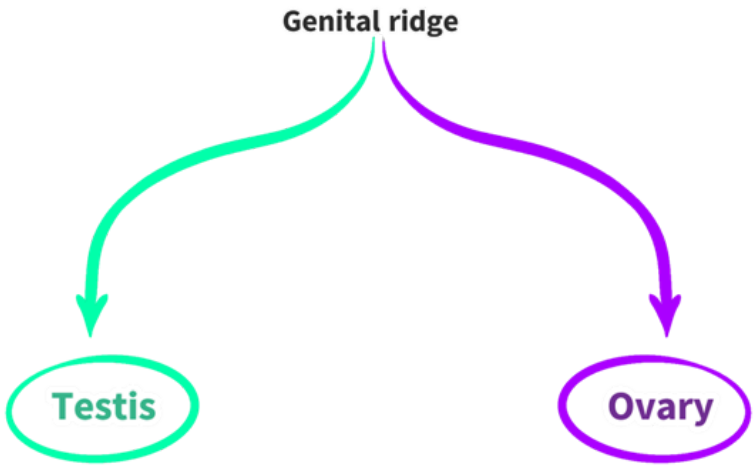
Molecule/ gene	Role in Sex Determination
WNT4	Promotes ovarian development. Activates the female pathway, contributing to the formation of ovaries and female reproductive structures. "A mutation in the WNT4 gene has been found to cause a severe condition called SERKAL (SEx Reversal and abnormal development of Kidneys, Adrenals, and Lungs) syndrome. In this condition, male sex development may occur despite the chromosome pattern typical of females." https://medlineplus.gov/genetics/gene/wnt4/#:~:text=A%20mutation%20in%20the%20WNT4,chromosome%20pattern%20typical%20of%20females.
SRY gene	Main regulator of male sex determination. Activates the male pathway, leading to testicular development and production of male sex hormones. "Variants (also called mutations) in the SRY gene have been identified in approximately 15 percent of individuals with Swyer syndrome, also known as 46,XY complete gonadal dysgenesis or 46,XY pure gonadal dysgenesis. Swyer syndrome is a condition that affects sex development. Individuals with this condition have a male-typical chromosome pattern (46,XY karyotype), but they develop female-typical sex characteristics. Also related to testicular difference of sex development where a 46,XX fetus will develop male characteristics". https://medlineplus.gov/genetics/gene/sry/#conditions
CYP21A2 gene	Encodes enzyme 21-hydroxylase. Mutations can cause congenital adrenal hyperplasia (CAH), affecting cortisol production and sex determination. "All types of 21-hydroxylase deficiency interfere with the production of cortisol and aldosterone. The substances that are usually used to form these hormones instead build up in the adrenal glands and are converted to androgens, which are male sex hormones. The excess production of androgens leads to abnormalities of sexual development in people with 21-hydroxylase deficiency". https://medlineplus.gov/genetics/gene/cyp21a2/#conditions

AR gene	**Encodes androgen receptor protein**. Mutations can cause androgen insensitivity syndrome (AIS), leading to varying degrees of feminization of external genitalia. "People with this condition are genetically male, with one X chromosome and one Y chromosome in each cell. Because their bodies are unable to respond to androgens, they may have mostly female sex characteristics or signs of both male and female sexual development." https://medlineplus.gov/genetics/gene/ar/#conditions
SRD5A2 gene	**Encodes enzyme 5-alpha-reductase type 2**. Mutations can cause 5-alpha-reductase deficiency, resulting in ambiguous or female-appearing external genitalia. "As a result of SRD5A2 mutations, the body cannot effectively convert testosterone to DHT in reproductive tissues. People with 5-alpha reductase deficiency are genetically male, with one X and one Y chromosome in each cell, but they may be born with external genitalia that look predominantly female, or that are not clearly male or clearly female. Certain normal variations (polymorphisms) in the SRD5A2 gene may be associated with prostate cancer." https://medlineplus.gov/genetics/gene/srd5a2/#conditions
AMH/ AMHR2	**Anti-Müllerian hormone + receptor type 2**. Produced by testes, inhibits development of Müllerian ducts. Mutations in AMHR2 can cause retention of the Müllerian ducts despite having male reproductive organs. "Persistent Müllerian duct syndrome type 2, a disorder of sexual development that affects males, is caused by mutations in the AMHR2 gene. Males with this condition have female reproductive organs in addition to normal male reproductive organs." https://medlineplus.gov/genetics/gene/amhr2/#conditions

SOX9	**Transcription factor involved in testis development**. Upregulated by SRY gene, essential for testicular development and male sex determination. "Related health conditions such as 46,XX testicular difference of sex development and Swyer syndrome" https://medlineplus.gov/genetics/gene/sox9/#conditions
β-catenin	**Cell signalling molecule.** Plays a role in the activation of the female pathway and the suppression of the male pathway.
FGF9	**Fibroblast Growth Factor 9**. Secreted protein involved in the development of testes and the maintenance of the male reproductive system
ERa	**Oestrogen receptor alpha**. Receptor for oestrogen hormones, involved in the differentiation and development of female reproductive tissues
ERb	**Oestrogen receptor beta**. Receptor for oestrogen hormones, involved in the regulation of female reproductive functions and behaviour

Exercise 1:

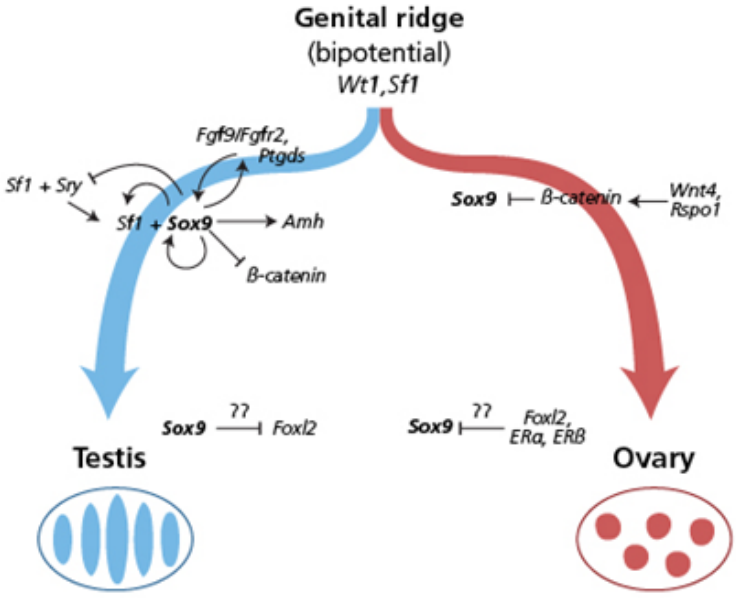
From the list above, where in this diagram would you put WNT4, SRY and SOX9 to obtain a typical biological female and male?

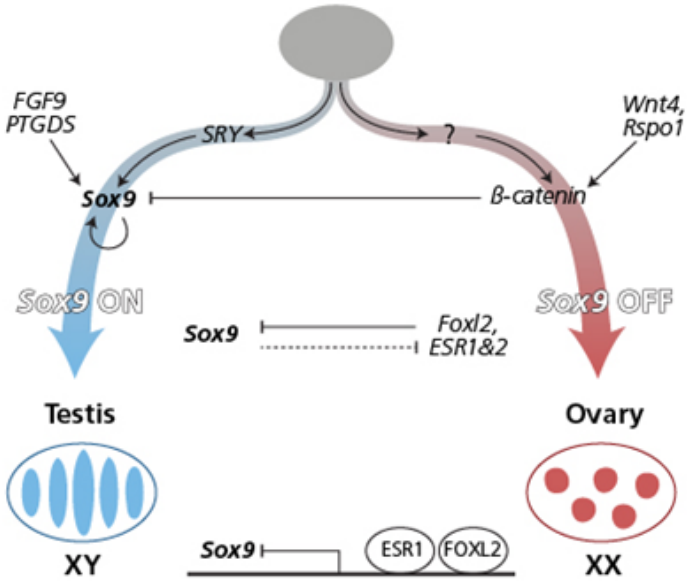


1 Adapted from The Genetics of Sex Determination: Rethinking Concepts and Theories

Now on your annotated diagram, answer this question: Where would AMH/AMHR2, SRD5A, b-catenin, FGF9 and ESR1/2 interact to cause atypical biological female and male characteristics? You can annotate interactions between the molecules themselves.

[ANSWER];





Exercise 2:

Using small post-its on an A4, label the A4 from typically biological male or female in a spectrum. (See the article on visualising sex as a spectrum).
In each post-it have the following genetic "conditions":

- *46XY + AR mutation*
- *46XX + SRY gene may be present*
- *45X*
- *46XX + CYP21A2 gene mutation*
- *45X/46XY mosaicism*
- *46XY + CYP21A2 gene mutation*
- *46XY + AMH mutation*
- *SRY gene*
- *46XX + WNT4 gene + absence of SRY gene*

Where in the sex spectrum do you think each condition fits?

Takeaways

- Sexual differentiation of the brain occurs during a critical period, with males and females showing differences in brain structures and functions.
- Testosterone and its metabolites play a crucial role in sex-dependent brain development through downstream signalling cascades and epigenetic events.
- Viewing sex differences in the brain as a spectrum, rather than a binary classification, is important for understanding the development of sex-biased psychopathology.
- Disorders of sex development (DSD) require a precise understanding of the underlying genetic characteristics and alterations to improve diagnosis and categorisation.

- Hormones and genetic factors interact in complex ways during psychosexual development and gender identity formation.
- The genetics of sex determination in humans differ from mice and involve various genes, including NR5A1, MAP3K1, GATA4, FOG2, SOX9, SOX3, and OVARYSOX10.
- Sex should be seen as a spectrum, including intersex individuals, transsexual, transgender individuals, and non-binary individuals, challenging rigid binary categorisations.
- Epigenetic patterns in the brain contribute to sex differences in cognitive and endocrine functions.
- Disorders of sex development highlight the transcriptional autonomy of genetic sex and the influence of androgen-programmed hormonal sex.
- Understanding the nuances of sex development could help scientists and the general population shed light on the relationship between sex and gender expression.

SEX AND GENDER IN THE POSTGENOMIC ERA

MELANIE GOISAUF, KAYA AKYÜZ

BBMRI-ERIC

Introduction

With the advance of genomics, specific individual conditions have received increased attention in the generation of scientific knowledge. As the field of genomics is progressing rapidly, it is important to discuss and reflect on the social configurations that are inscribed in, and reproduced by, genomic data-driven research and how the complexity of the social configurations are reduced through specific data practices in research. Starting from a critical view on how sex and gender categorisations were used in research on the genetics of same-sex sexual behaviour, this chapter aims to foster the understanding of the uses of sex and gender in other areas of genomics.

Selected resources

- Goisauf, M., Akyüz, K., & Martin, G. M. (2020). Moving back to the future of big data-driven research: reflecting on the social in genomics. Humanities and Social Sciences Communications, 7(1), 55. doi:10.1057/s41599-020-00544-5

The article discusses a large-scale genome-wide association study (GWAS) on sexual orientation that suggested a partial genetic basis for same-sex sexual behaviour. It critically reflects on how in the process of datafied genomics research, societal relations, understandings and categorisations (i.e., sex and gender) are used and inscribed into social phenomena and outcomes. In doing so, the article shows how underlying classification and categorisations, which are inherently social in their production, can have wide ranging implications.

- Ussher, J. M. (2010). Are We Medicalizing Women's Misery? A Critical Review of Women's Higher Rates of Reported Depression. Feminism & Psychology, 20(1), 9-35. doi:10.1177/0959353509350213

This paper is a critical review of women's higher rates of reported depression, examining the question of whether women's misery is being medicalised. It explores the intersection of gender, mental health, and medicalisation within the context of depression.

- Richardson, S. S. (2012). Sexing the X: How the X Became the "Female Chromosome". Signs: Journal of Women in Culture and Society, 37(4), 909-933. doi:10.1086/664477

This paper explores the history and cultural construction of the X chromosome as the "female chromosome," examining how the X chromosome became associated with femaleness. It delves into the gendering of genetics and its implications.

- Web resources:

  - Gendered Innovations resource for Nutrigenomics as a case
  - BBMRI-ERIC webinar on "Visualizing Complexity of Sex Determination"
  - BBMRI-ERIC webinar on "The Importance of Sex and Gender for Biomedical Research"

Proposed didactic activities

Step 1: How do data practices impact the research outcomes?

- With the paper Goisauf, Akyüz & Martin, 2020, discuss how data practices in genomics have an impact on knowledge produced. As this paper focuses on a same-sex sexual behaviour from a genomics perspective, it also shows how to critically think about any genomics research that involves categorisations of humans, setting an example for the group discussion in Step 3.

  - Resource: Goisauf, M., Akyüz, K., & Martin, G. M. (2020). Moving back to the future of big data-driven research: reflecting on the social in genomics. Humanities and Social Sciences Communications, 7(1), 55. doi:10.1057/s41599-020-00544-5

  - You may find the following ontology useful to raise further thoughts on other potential categorisations that do or do not reflect social complexity: https://www.ebi.ac.uk/ols/ontologies/gsso

- Holterhus, P. M., Bebermeier, J. H., Werner, R., Demeter, J., Richter-Unruh, A., Cario, G., . . . Hiort, O. (2009). Disorders of sex development expose transcriptional autonomy of genetic sex and androgen-programmed hormonal sex in human blood leukocytes. BMC Genomics, 10, 292. doi:10.1186/1471-2164-10-292.

The paper analyses different components of gender during development and embryonic programming with a focus on DSD. However, this paper considers gender as the expression of the sexual characteristics. Differences in expression arise during embryogenesis and are caused by a combination of sex chromosomes, hormonal programming, and the androgen milieu.

Step 2: Differences, Sex and Gender: Nutrigenomics as a case

- Based on Gendered Innovations, read about and contemplate why for nutrigenomics, taking into account sex and gender is relevant.

  - Resource: Gendered Innovations resource for Nutrigenomics as a case

Step 3: Break-out group discussions

- Within a break-out group, take one of the suggested articles below or any other article in the field of nutrigenomics that you identify yourself and critically think about the data practices regarding sex and gender. Examples to nutrigenomics papers that can be critically analysed are:

  - Nakamura, S., Fang, X., Saito, Y., Narimatsu, H., Ota, A., Ikezaki, H., . . . Wakai, K. (2023). Effects of gene–lifestyle interactions on obesity based on a multi-locus risk score: A cross-sectional analysis. PLoS One, 18(2), e0279169. doi:10.1371/journal.pone.0279169

  - Surendran, S., Aji, A. S., Ariyasra, U., Sari, S. R., Malik, S. G., Tasrif, N., . . . Vimaleswaran, K. S. (2019). A nutrigenetic approach for investigating the relationship between vitamin B12 status and metabolic traits in Indonesian women. J Diabetes Metab Disord, 18(2), 389-399. doi:10.1007/s40200-019-00424-z

- The following questions may be helpful:

  - Is the data used already collected or collected for the research itself?
  - Is there a bias in research design regarding sex and gender?
  - Which societal/biological groups are excluded in categorisations and why?
  - What problems do you see in the generalisation of findings for the broader society? Any risks for social equality in health?

Takeaways

- Research should better reflect on how the social and the biological interact in scientific knowledge production, and how sex and gender are (re-)produced in doing research with data, especially in health research.

- There is no "raw" data, but data is always shaped by social aspects, societal contexts, and scientific practices, which better equips researchers to identify potential biases.

- Research should better reflect on the critical decision making in translating social/demographics into data, especially inclusion and exclusion, and ways of conducting more inclusive research and responsible data practices.

SEX AND GENDER DIMENSION IN THE CATEGORISATION USED IN THE LIFE SCIENCES

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Introduction

In life sciences, categorisations based on sex and gender play a significant role in understanding various aspects and the gender/sex differences demonstrated in health, disease, and treatment outcomes. However, limitations arising from treating sex and gender as binary categories have revealed a strong need for more nuanced understanding and terminology.

Assuming that sex and gender are binary, and individuals perfectly fit onto one of those two categories is an oversimplified approach and it does not capture the diversity nor fluidity of humans and their experiences. These experiences affect behaviour as well as biological variants such as risk factors for diseases, protective effects, etc. Social sciences have already taken steps towards demonstrating that sex and gender are not rigid nor are they binary, rather they exist on a fluid spectrum. Although individuals categorise themselves in a male-female binary, their day-to-day life is greatly affected by their gender identity.

Research articles such as "Transcending the Male-Female Binary in Biomedical Research: Constellations, Heterogeneity, and Mechanism When Considering Sex and Gender" and "Sex Trouble: Sex/Gender Slippage, Sex Confusion, and Sex Obsession in Machine Learning Using Electronic Health Records" highlight the challenges and false assumptions associated with binary sex and gender categorisations. These articles emphasise the need for a more comprehensive understanding of sex and gender to avoid perpetuating harm and to ensure accurate representations in medical research and machine learning algorithms.

Moreover, studies like "Masculine Gender Affects Sex Differences in the Prevalence of Chronic Health Problems - The Doetinchem Cohort Study" and "Does Gender Role Explain a High Risk of Depression? A Meta-Analytic Review of 40 Years of Evidence" reveal the influence of gender on health outcomes. Gender is a relevant component in understanding and addressing sex differences in various health conditions, highlighting the inadequacy of the actual binary categorisation.

The differences between sex and gender hold great significance in all areas of life sciences. It is crucial to examine and redefine these categorisations as a means of accounting for the complexities and variations present in each individual. If we were able to achieve this goal, we could foster much more inclusive research, precise diagnosis, and accurate treatment practices that better serve individuals.

Selected resources

Relevance of changes in categorisations since they are not as binary as thought in many different medical fields:

- Ritz, S. A., & Greaves, L. (2022). Transcending the Male-Female Binary in Biomedical Research: Constellations, Heterogeneity, and Mechanism When Considering Sex and Gender. Int J Environ Res Public Health, 19(7). doi:10.3390/ijerph19074083.

This paper explores the challenges of incorporating sex and gender factors in health research and proposes a more nuanced approach.

- Albert, K., & Delano, M. (2022). Sex trouble: Sex/gender slippage, sex confusion, and sex obsession in machine learning using electronic health records. Patterns (N Y), 3(8), 100534. doi:10.1016/j.patter.2022.100534.

The paper discusses the false assumption that sex and gender are binary and static in the medical system. It also explores different methods to understand and address incorrect representations to avoid perpetuating harm and stereotypes. The paper discusses "sex/gender slippage," "sex confusion," and "sex obsession" and explores their impact in medical machine learning research.

It provides recommendations for machine learning researchers to engage more thoughtfully with sex and gender questions.

Cancer

- Irelli, A., Sirufo, M. M., D'Ugo, C., Ginaldi, L., & De Martinis, M. (2020). Sex and Gender Influences on Cancer Immunotherapy Response. Biomedicines, 8(7). doi:10.3390/biomedicines8070232.

This paper is a review of the available knowledge on the role of sex and gender in cancer immunotherapy and offers ideas on how to enhance the understanding and practice of the clinicians and researchers in the inclusion of the gender perspective in new cancer treatment strategies.

It also highlights the lack of literature on gender in cancer and how that creates a burden when considering cancer treatment and therapies.

Neurobiology and degenerative diseases

- Roselli, C. E. (2018). Neurobiology of gender identity and sexual orientation. J Neuroendocrinol, 30(7), e12562. doi:10.1111/jne.12562.

This is a review of the relationship between sexual identity and orientation and how they shape one's brain development as well as sexual behaviour.

No clear 'conclusion' but the data reviewed suggest a relation between early development and sexual identity and orientation.

Mental health

- Tsirigotis, K., Gruszczyński, W., & Tsirigotis-Maniecka, M. (2014). Gender differentiation in indirect self-destructiveness and suicide attempt methods (gender, indirect self-destructiveness, and suicide attempts). Psychiatr Q, 85(2), 197-209. doi:10.1007/s11126-013-9283-1.

The paper studies the gender/sex differentiation of indirect self-destructiveness (behaviours that inflict negative effects either immediately or in the long run) and the correlation with the chosen methods when attempting suicide. The sample of the study is 147 people (114 females, 33 males).

There is a generalised misconception that men suffer more mentally since they have a higher rate of suicides. The variables considered (indirect self-destructiveness, risks, poor health maintenance, lack of playfulness and helplessness) showcase that the red flags' can appear differently depending on the gender.

- Lin, J., Zou, L., Lin, W., Becker, B., Yeung, A., Cuijpers, P., & Li, H. (2021). Does gender role explain a high risk of depression? A meta-analytic review of 40 years of evidence. J Affect Disord, 294, 261-278. doi:10.1016/j.jad.2021.07.018.

Categorising gender roles as binary is inadequate. The paper concludes that androgynous individuals have lower depression rates. Masculinity is protective against depression regardless of gender, but its dominance has declined with increasing life expectancy. Femininity becomes protective with higher education and income levels. Androgyny appears to be the most ideal gender role for preventing depression in both women and men.

- McCrossin, R. (2022). Finding the True Number of Females with Autistic Spectrum Disorder by Estimating the Biases in Initial Recognition and Clinical Diagnosis. Children (Basel), 9(2). doi:10.3390/children9020272.

The article investigates biases in diagnosing autism spectrum disorder (ASD) in females and suggests that the commonly quoted 4:1 male-to-female ratio may underestimate the true ratio. The study identifies and quantifies biases, finding that 80% of females remain undiagnosed by age 18, impacting their mental health.

Microbiology and derived diseases

- Dias, S. P., Brouwer, M. C., & van de Beek, D. (2022). Sex and Gender Differences in Bacterial Infections. Infect Immun, 90(10), e0028322. doi:10.1128/iai.00283-22.

Sex and gender have significant influences on pathophysiology, clinical presentation, treatment response, and outcome. Factors such as genetic, immunological, hormonal, and behavioural differences contribute to these disparities. Gender roles and access to healthcare also impact disease patterns.

Cardiology

- Regitz-Zagrosek, V., & Gebhard, C. (2023). Gender medicine: effects of sex and gender on cardiovascular disease manifestation and outcomes. Nat Rev Cardiol, 20(4), 236-247. doi:10.1038/s41569-022-00797-4.

This review showcases examples from cardiovascular diseases where gender and sex variables have opposite effects, especially in the case of women assigned at birth on individual health.

Reaction to pharmacological drugs

- Greenspan, J. D., Craft, R. M., LeResche, L., Arendt-Nielsen, L., Berkley, K. J., Fillingim, R. B., . . . Traub, R. J. (2007). Studying sex and gender differences in pain and analgesia: a consensus report. Pain, 132 Suppl 1(Suppl 1), S26-s45. doi:10.1016/j.pain.2007.10.014.

This 2006 review highlights the gender differences when it comes to pain and analgesia and is aimed to work as a guide for research in the future. It intends to respond to the question "Do I really need to study females?". It includes a whole section on "Translational considerations for the study of sex differences in pain and analgesia" and "Future directions" where a discussion is introduced on how even psychological factors such as stress can contribute to this difference in resistance and tolerance.

Proposed didactic activities

Interactive Visualisation: "Sex and Gender Infographic"

- Divide the participants into small groups of 2-4 and provide them with an A3 and markers (they require access to the internet as well, or some source material i.e., some of the articles included in this document).

- Each group will get a topic in life sciences (e.g., cardiology, oncology, endocrinology) and will research how sex and gender have an impact in each field (e.g., in cardiology being female is a protective factor against adverse events occurring while being a woman is negatively associated).

    - Impact of sex and gender in the Field
    - Is this field of medicine considered generally binary? Is gender normally taken into account?
    - Potential benefits and limitations of the inclusion of sex and gender dimensions in this field
    - Future perspectives: Is there a way you would change the categorisations or include the sex and gender perspective in order to make studies more inclusive?

- Each group has to create a simple graphic poster that highlights the importance of including sex and gender in the categorisations of life sciences and why (diagrams and drawings are highly recommended for the activity).

- The activity in total should be 40 minutes.

- After the time is up, ask each group to present their infographic to the rest of the participants, explaining the key concepts and insights portrayed, 2-3 minutes per group.

- After the time is up, ask each group to present their infographic to the rest of the participants, explaining the key concepts and insights portrayed, 2-3 minutes per group.

    - Did they understand the differences between sex and gender?
    - Does the inclusion of sex and gender have the same impact in all the fields?
    - Are the binary categorisations static or should we switch to a continuum spectrum of sex and gender? Why?

- Write up **conclusions** from the participants for future trainings.

Takeaways

- Categorisations in medical research should go beyond the male-female and women-men binary, considering the complexity of sex and gender in human experiences.
- The assumption of sex and gender as binary in healthcare can be harmful, and addressing incorrect representations is crucial for inclusive practices.
- Sex and gender differences have significant implications in microbiology, cardiovascular diseases, and response to pharmaceutical treatments. Genetic, immunological, hormonal, behavioural, and healthcare access factors contribute to disparities in disease patterns and outcomes.

INTEGRATING INTERSECTIONALITY IN THE LIFE SCIENCES

MÓNICA CANO ABADÍA

BBMRI-ERIC

Introduction

Intersectionality is a theoretical framework rooted in the premise that human experience is jointly shaped by multiple social positions (e.g., race, gender), and cannot be adequately understood by considering social positions independently. First published by legal scholar Kimberlé Crenshaw and developed within Black feminist theory to better explicate the situation of Black women in the U.S., it is extendable to a wide range of intersections of ethnoracial groups, gender, socioeconomic status, sexual orientation, and other social identities or positions. As social positions intersect at the individual level (e.g., race and gender), experiences at those intersections are influenced by larger interpersonal and structural systems of oppression such as racism and sexism.

Studies on how socially disadvantaged individuals get grouped together into larger, less precise categories and how they, therefore, suffer from inadequate organisational practices have been primarily influenced by intersectionality theory. A wider range of actors and organisational contexts, including professionals and elites, can benefit from the general tenet of intersectionality theory, which holds that social identities and subjectivities are composed of diverse and occasionally even antagonistic and/or colliding elements, leading to fragmented yet coherent, or at least functional, subject-positions.

Recognising the importance of integrating these analytics into research from the very beginning, the European Commission strengthened its "gender dimension" in research requirements in 2020.1 The Commission states that integrating sex, gender, and/or intersectional analysis is "mandatory" across "all Work Programmes, destinations and topics, unless its non-relevance for a specific topic is specified in the topic description."

The project Gendered Innovations proposes intersectionality as one of the keystones of strategies on the integration of sex and gender in research. Applying an intersectional approach requires analysing not only sex and gender but also how these traits of identity intersect with other relevant factors such as race, ethnicity, age, ability, etc. The assessment of which factors are relevant in each case is necessary to apply this perspective successfully. An embedded ethics approach, which incorporates the collaboration of scientists, ethicists, lawyers, social scientists, etc., within interdisciplinary teams is an interesting way to incorporate this perspective.
See the Gendered Innovations website to see how to integrate an intersectional perspective in different phases: identifying the problems, research design, data collection, data analysis, and dissemination and reporting of results.

Selected resources

- Crenshaw, K. W. (1989). Demarginalizing the Intersection of Race and Sex: A Black Feminist Critique of Antidiscrimination Doctrine, Feminist Theory and Antiracist Politics. U. Chi. Legal. F., 139.

Foundational work of legal theorist Kimberlé Crenshaw, who coined the term of intersectionality and showed in this paper how gender and race intersect with each other to affect black women's lives in a very specific way.

- Simien, E. M. (2007). Doing Intersectionality Research: From Conceptual Issues to Practical Examples. Politics & Gender, 3(2), 264-271. doi:10.1017/S1743923X07000086

The goal of this essay is to highlight both conceptual issues and practical examples of intersectionality research.

- Styhre, A. (2018). Intersectionality and professional work in the life sciences: Constructing identities on the basis of affirmation, dis-identification, and professional distancing. ephemera, 18 (1), 51-79.

This paper showcases a detailed understanding of how professional identities and their ethos are constructed on the basis of heterogeneous resources and existing institutional and organisational arrangements, in turn having implications for life science innovation.

- Kozlowski, D., Larivière, V., Sugimoto, C. R., & Monroe-White, T. (2022). Intersectional inequalities in science. Proc Natl Acad Sci U S A, 119(2). doi:10.1073/pnas.2113067119

Most studies have looked at either race or gender, failing to account for the intersection of these variables. Their analysis utilises millions of scientific papers to study the relationship between scientists and the science they produce, accounting for the intersection between race and gender.

- Kelly, U. A. (2009). Integrating intersectionality and biomedicine in health disparities research. ANS Adv Nurs Sci, 32(2), E42-56. doi:10.1097/ANS.0b013e3181a3b3fc

This study provides a practical application of the integration of biomedical and feminist intersectionality paradigms in nursing research, using a psychiatric intervention study with battered Latino women as an example.

- Buchanan, N. T., & Wiklund, L. O. (2021). Intersectionality Research in Psychological Science: Resisting the Tendency to Disconnect, Dilute, and Depoliticize. Res Child Adolesc Psychopathol, 49(1), 25-31. doi:10.1007/s10802-020-00748-y

In this article the authors review intersectional theory and praxis, examine psychological science and its resistance to fully incorporating intersectionality, and highlight how research must shift to be truly intersectional.

- Schiebinger, L. (2022). Sex, gender, and intersectional puzzles in health and biomedicine research. Med, 3(5), 284-287. https://doi.org/10.1016/j.medj.2022.04.003

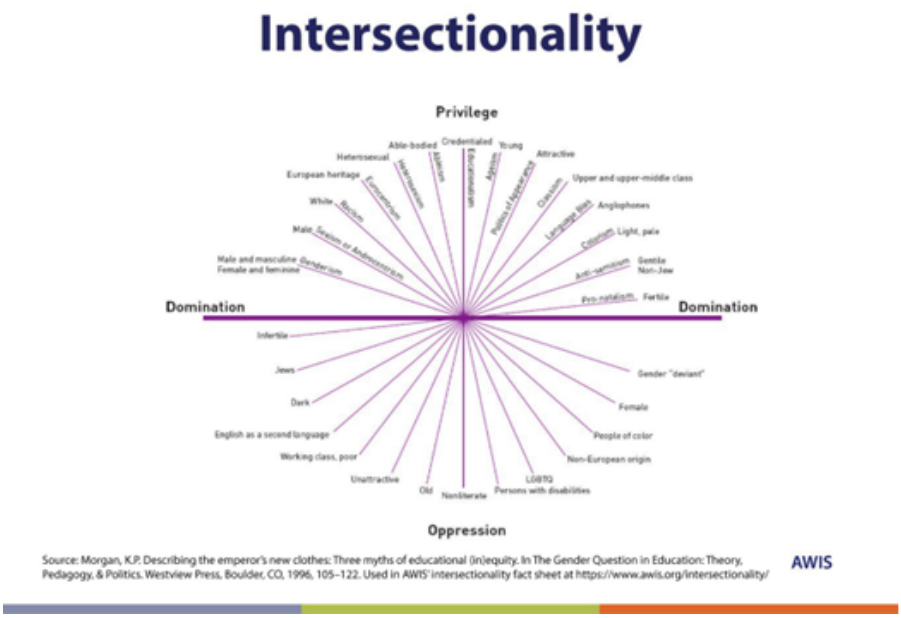
Excellent research integrates sex, gender, and/or intersectional analysis—from the very beginning and throughout the research process. This article highlights techniques for analysing sex, how sex and sex interact, how sex and gender interact, and the need for intersectional analysis. Designing sex, gender, and intersectional analysis into research is one crucial component contributing to world-class health and biomedicine.

- Canfield, K. N., Menezes, S., Matsuda, S. B., Moore, A., Mosley Austin, A. N., Dewsbury, B. M., . . . Taylor, C. (2020). Science Communication Demands a Critical Approach That Centers Inclusion, Equity, and Intersectionality. Frontiers in Communication, 5. doi:10.3389/fcomm.2020.00002

Science communication practitioners and scholars need to consider how identities operate not only interpersonally, but also systemically. The authors advocate for intersectional science communication as a critical approach that embodies an intentional investment in supporting and recognising inclusion, equity, and intersectionality from ideation to implementation and evaluation.

Proposed didactic activities

- Discuss the chart of intersectionality traits in groups of 3-5 persons.



- Are there other traits of identity that do not appear on the chart?

Takeaways

- Intersectionality is a theoretical framework rooted in the premise that human experience is jointly shaped by multiple social positions (e.g., gender, race, age) that are context-dependent.
- The European Commission states that integrating sex, gender, and/or intersectional analysis is "mandatory" across "all Work Programmes".
- Applying an intersectional approach requires analysing not only sex and gender but also how these traits of identity intersect with other relevant factors such as race, ethnicity, age, ability, etc.
- The assessment of which factors are relevant in each case is necessary to apply this perspective successfully. Interdisciplinary teams which integrate scientists, social scientists, ethicists, etc., are useful to perform this assessment.

INTEGRATING THE SEX AND GENDER DIMENSION IN STUDY DESIGN

FATEMEH BAGHDADI, MARÍA FLORES

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Introduction

Sex and gender dimensions play a crucial role in research design across various scientific disciplines, particularly in the field of biomedical research. As time goes by, more and more literature emphasises the need to integrate sex and gender considerations into study design to improve the accuracy and applicability of research findings.

The articles presented will highlight the consequences of overusing male models, misconceptions regarding male bias, the development of toolkits and methodologies to integrate sex and gender, and the role of funding agencies in promoting the integration of sex and gender. Additionally, they offer practical tips, metrics, and approaches for researchers to enhance the integration of sex and gender in their studies. By integrating sex and gender dimensions, researchers can achieve more robust and equitable scientific outcomes that better address the diversity of human health.

Selected resources

- Ritz, S. A., Antle, D. M., Côté, J., Deroy, K., Fraleigh, N., Messing, K., . . . Mergler, D. (2014). First steps for integrating sex and gender considerations into basic experimental biomedical research. Faseb j, 28(1), 4-13. doi:10.1096/fj.13-233395

The paper presents a discussion on how social beliefs and inner biases lead to wrong hypotheses regarding diseases. It presents the overuse of male models and highlights the complications when integrating sex and gender when using in vitro and animal models. It also provides a toolbox on how to include sex and gender in your research.

- Incorporating the sex and gender perspective in research content: a toolkit.

This practical toolkit guides readers with a questionnaire through the process of incorporating the sex and gender perspective in research content, paying attention to certain aspects:

The relevance of integrating sex and gender: Because to standardise results, studies were performed mainly in male specimens. This contradicts evidence-based health in the case of women.

Male bias misconception: choose male specimens to avoid possible variability due to cyclically fluctuating hormones and the belief that there are no major differences aside from sexual characteristics and chromosomes.

- Mason, R. (2020). Doing better: eleven ways to improve the integration of sex and gender in health research proposals. Research Integrity and Peer Review, 5(1), 15. doi:10.1186/s41073-020-00102-2

This paper provides eleven tips on how the integration can be done for researchers that are unsure of how to proceed and follows the logic of a scientific study (from background literature to the dissemination and even team description).

- Day, S., Mason, R., Tannenbaum, C., & Rochon, P. A. (2017). Essential metrics for assessing sex & gender integration in health research proposals involving human participants. PLoS One, 12(8), e0182812. doi:10.1371/journal.pone.0182812

This paper outlines essential metrics for health researchers and funding bodies to use in order to integrate considerations of sex and gender into research proposals. They emphasise the importance of understanding the differences between sex and gender and how their relevance varies depending on the study. These metrics are useful not only for studies that investigate sex/gender differences but also for within-group differences in sex- or gender-specific studies.

- Johnson, J. L., Greaves, L., & Repta, R. (2009). Better science with sex and gender: Facilitating the use of a sex and gender-based analysis in health research. International Journal for Equity in Health, 8(1), 14. doi:10.1186/1475-9276-8-14

The authors developed a primer to provide detailed definitions of sex and gender, discuss a sex and gender-based analysis (SGBA), and suggest three approaches for incorporating sex and gender in health research at various stages of the research process. (Although it's a paper from 2009). It includes the case study of a knee injury.

- Nieuwenhoven, L., & Klinge, I. (2010). Scientific excellence in applying sex- and gender-sensitive methods in biomedical and health research. J Womens Health (Larchmt), 19(2), 313-321. doi:10.1089/jwh.2008.1156

The work presented in this article is based on the contents of a workshop (published in 2010) that aimed at familiarising researchers with the basics of conducting sex- and gender-sensitive research. It provides an introduction to sex- and gender-sensitive methods and a tool presented that allows for the detection of sex and gender bias throughout all phases of the research process. Solutions proposed in:

- Relevance checking
- Literature search
- Formulation of research questions and hypotheses
- Research methods and samples
- Data analysis and interpretation
- Reporting

- Conclusions and recommendations.

- Haverfield, J., & Tannenbaum, C. (2021). A 10-year longitudinal evaluation of science policy interventions to promote sex and gender in health research. Health Research Policy and Systems, 19(1), 94. doi:10.1186/s12961-021-00741-x

This paper presents a 10-year longitudinal evaluation of science policy interventions aimed at promoting the consideration of sex and gender in health research. It provides an overview of interventions implemented by the Canadian Institutes to increase the uptake of sex and gender in grant applications. It presents quantitative data on the trends in sex and gender uptake in grant applications and the associations between the sex of the applicant and the uptake of sex and gender, and the latter with funding success.

It highlights the importance of discipline-specific training, and tailored coaching, which could be valuable information for workshop attendees who are interested in learning how to effectively integrate sex and gender in their research.

- Lee, S. K. (2018). Sex as an important biological variable in biomedical research. BMB Rep, 51(4), 167-173. doi:10.5483/bmbrep.2018.51.4.034

This is a review of the organisations that want to propose the use of sex and gender as variables, why and how they take action. It provides more detail about specific strategies and guidelines such as SABV, ARRIVE and other initiatives taken by e.g., JNR, IMCJE. They claim: "We do not only want to know if there are sex differences, we also need to know when there are not differences and under what conditions."

- Bauer, G. R., Braimoh, J., Scheim, A. I., & Dharma, C. (2017). Transgender-inclusive measures of sex/gender for population surveys: Mixed-methods evaluation and recommendations. PLoS One, 12(5), e0178043. doi:10.1371/journal.pone.0178043

This paper presents a mixed-methods evaluation and recommendations for transgender-inclusive measures of sex/gender for population surveys. It aims to improve the inclusivity and accuracy of sex and gender measures in survey research. Recommendations include a new multidimensional sex/gender measure with three simple items and optional additions for comprehensive analysis. Adaptation considerations are provided for different contexts.

- Raparelli, V., Santilli, F., Marra, A. M., Romiti, G. F., Succurro, E., Licata, A., . . . Basili, S. (2022). The SIMI Gender '5 Ws' Rule for the integration of sex and gender-related variables in clinical studies towards internal medicine equitable research. Intern Emerg Med, 17(7), 1969-1976. doi:10.1007/s11739-022-03049-y

This paper introduces the SIMI Gender '5 Ws' Rule for integrating sex and gender-related variables in clinical studies, aiming for equitable research in internal medicine. It outlines a framework to guide the incorporation of sex and gender considerations in clinical research to promote equity.

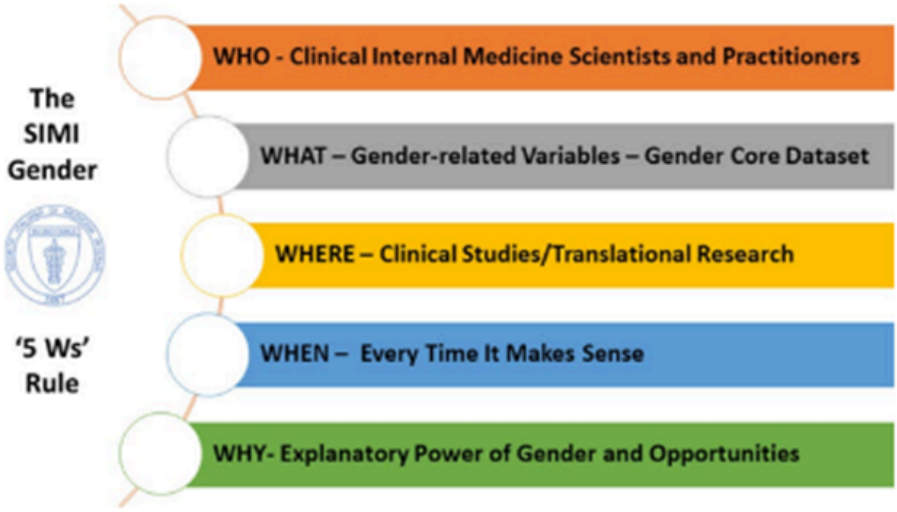

Fig. 1 The SIMI Gender '5 Ws' Rule for clinical studies

Canadian investigators collected gender-relevant variables through a questionnaire and developed a methodology to generate a composite measure of gender, the gender score. This score predicted the recurrence of cardiovascular events and showed that individuals with characteristics traditionally ascribed to women had worse outcomes, highlighting the importance of including gender and sex in studies. (Includes gender composite score and its risks).

Proposed didactic activities

Background reading (not required): Ritz, S. A., Antle, D. M., Côté, J., Deroy, K., Fraleigh, N., Messing, K., . . . Mergler, D. (2014). First steps for integrating sex and gender considerations into basic experimental biomedical research. Faseb j, 28(1), 4-13. doi:10.1096/fj.13-233395

- Why can't results obtained from studies with a majority of subjects from one gender be extrapolated to others?
    - Answer: Diverse factors (social dynamics, occupation, and physical activity) can influence biological traits. The biases regarding gender roles and stereotypes are present when developing theories in reproductive biology and neurobiology.
- What is the sex-gender distinction, and why was it developed?
    - Answer: This distinction was created to challenge biological determinist views of all the differences between men and women. While the concepts of sex and gender can be distinguished, they are not always neatly separated in practice. For example, many studies using mice report gender instead of sex (which could be considered bad practice or misuse of the term).

- Can in vitro studies of isolated cells reveal all the sex differences that affect the topic of interest?
    - Answer: No. Studying isolated cells in a laboratory setting can only uncover sex differences that result from genetic makeup or past cell conditioning. We cannot assume that differences observed in vitro are biologically based because they may be due to societal differences in exposure.
- Why is obtaining equivalent male and female research animals not always simple, and what are the implications of this?
    - Answer: For some models, male or female animals may not be viable or the disease may not manifest in one sex. Male animals are used more often than females in most fields of study, which could be due to cost. The incorporation of sex considerations into laboratory-based cell and animal research is not simple and straightforward and may have significant practical and financial implications.
- How would you tackle sex and gender inclusion throughout your study?
    - Answer:
        - Develop knowledge of the sex and gender issues on that topic (literature reviews, have a good understanding of sex and gender and don't use them interchangeably).
        - Report the sex/gender of the sample used. Justify the use of one or more sexes or genders, develop the limitations your choice has and discuss the possible implications of the results.
        - Conduct a pilot experiment (add hormones to cultures, include male and female, see if differences are reported).

Takeaways

- Social beliefs and inner biases can lead to wrong hypotheses regarding diseases. A frequent example of this is the overuse of male models (or exclusion of female models) in clinical studies.
- International funding agencies are putting policies and mechanisms in place to integrate sex and gender considerations in biomedical research.
- Gender-relevant variables need to be collected and used to develop a methodology to generate a composite measure of gender, the gender score.
- A tool has been developed that allows for the detection of sex and gender bias throughout all phases of the research process.
- There are methodological challenges in taking into account the interrelated biological and social dimensions of gender and their interactions in research on environmental health.

SEX AND GENDER DIMENSION IN SINGLE CELL MULTIOMICS

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Introduction

Sex-biased regulatory network structures have been described in healthy tissue as well as in diseased individuals. Even though most transcription factors (TFs) are not differentially expressed between males and females, many have sex-biased regulatory targeting patterns. For example, genes associated with Parkinson's disease and Alzheimer's disease are targeted by different sets of TFs in each sex (Lopes-Ramos et al. 2020)

The former is exemplified in this article where the authors find important transcriptional differences when stratifying the study by sex. The authors found important differences related to Alzheimer disease. This is of great importance when designing a study either in humans or in model organisms so the sex dimension is properly considered to account for these differences. Having this dimension in mind will fuel the development of therapies that may prove more effective at reversing Alzheimer's disease (AD) pathophysiology both in males and females appropriately (Belonwu et al. 2022).

Selected resources

- Belonwu, S., Li, Y., Bunis, D., Rao, A. A., Solsberg, C. W., Tang, A., . . . Sirota, M. (2022). Sex-Stratified Single-Cell RNA-SEQ analysis identifies Sex-Specific and cell Type-Specific transcriptional responses in Alzheimer's disease across two brain regions. Molecular Neurobiology, 59(1), 276–293. https://doi.org/10.1007/s12035-021-02591-8

This article explores sex-specific mechanisms in AD, revealing prominent differences in glial cells of the prefrontal cortex and opposing gene perturbations in the entorhinal cortex. These findings contribute to understanding AD-related transcriptomic changes and the development of more effective therapies.

- Lopes-Ramos, C. M., Chen, C. Y., Kuijjer, M. L., Paulson, J. N., Sonawane, A. R., Fagny, M., . . . DeMeo, D. L. (2020). Sex Differences in Gene Expression and Regulatory Networks across 29 Human Tissues. Cell Rep, 31(12), 107795. doi:10.1016/j.celrep.2020.107795

This article examines sex differences in gene regulation across human tissues, revealing sex-biased networks. These sex-specific processes influence tissue functions and diseases like Parkinson's and Alzheimer's. It highlights the importance of sex-specific gene regulation in health and disease.

Proposed didactic activities

Based on Lopes-Ramos et al. (2020):

- Why is studying sex differences in gene expression and gene regulatory networks important for understanding human diseases? Please provide reasons and examples to support your answer.
- What challenges exist in studying sex as a biological variable in research? How do these challenges impact research interpretation, and what are potential solutions?
- How do you think a better understanding of sex-specific gene regulation can contribute to precision medicine approaches and personalised treatments for individuals? Provide your insights or ideas on this topic.

Based on Belonwu et al. (2022):

- How was the sex stratification made?
- What are the main findings the authors made in terms of sex differences in Alzheimer disease patients?
- Two proteins are mentioned: LINGO1 and SPP1. Explain how differences in these gene expressions lead to sex differences in Alzheimer's disease. Which sex is more affected and why?

Takeaways

- Sex-biased regulatory network structures exist in both healthy and diseased individuals.
- Transcription factors (TFs) often show sex-biased regulatory targeting patterns, even when their expression levels are not significantly different between males and females.
- Diseases such as Parkinson's disease and Alzheimer's disease exhibit sex-specific regulatory differences, with different sets of TFs targeting genes associated with these diseases in each sex.
- Considering the sex dimension in research design, both in human studies and model organisms, is crucial to properly account for transcriptional differences and potential therapeutic implications.
- Understanding the sex-specific molecular regulation can lead to the development of more effective therapies to reverse the pathophysiology of diseases like Alzheimer's in both males and females.

INTEGRATING A GENDER- AND SEX-SENSITIVE DIMENSION INTO PHARMACEUTICALS

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Introduction

Pharmaceutical research, closely related to drug development, is a sub-field of biomedicine where the inclusion of the sex and gender perspective is urgent. Most of the treatments we have are the outcome of pre-clinical and clinical trials with a specific drug. For this, lack of gender diversity within these trials has resulted in suboptimal healthcare for minorities and females, which has been reported since 1986 (Geller et al., 2018). It is not acceptable to employ Caucasian male-tailored drug treatments, given the fact that the drug dynamics are quite different between males and females (Zucker & Prendergast, 2020).

This is due to many factors, but the most relevant one is argued to be the historically disproportionate use of male animal models in clinical trials (Zucker & Beery, 2010): A survey of 2000 animal studies published in 2010 found that 80% of studies had male bias (Ravindran et al., 2020).

There have been collective efforts to raise awareness regarding this bias. But, has this made an actual effect? Many meta-studies focus on the application of laws that require more diversity within clinical trials: from the NIH Revitalization Act of 1993 (Geller et al., 2018) to the NIH 2016 policy addressing historical over-representation of male subjects (Woitowitch et al., 2020). These differences arise in all three phases of the clinical trials and in both randomised and nonrandomised trials (Prakash et al., 2018).

Selected resources

- Tannenbaum, C., & Day, D. (2017). Age and sex in drug development and testing for adults. Pharmacological Research, 121, 83-93. https://doi.org/10.1016/j.phrs.2017.04.027.

This paper focuses on specific recommendations to include sex and age into different aspects of pharmaceuticals. It is ideal for the topic, has detailed tables and a comprehensive figure (See Fig.1.) that summarise these concrete actions to account for sex diversity within control trials.

These recommendations focus on: In vitro experiments, animal experiments, samples, all three phases of clinical trials, as well as for data collection.

- Avery, E., & Clark, J. (2016). Sex-related reporting in randomised controlled trials in medical journals. The Lancet, 388(10062), 2839–2840. https://doi.org/10.1016/S0140-6736(16)32393-5.

This journal article contains a review of 60 randomised control trails (RCTs), looking for 4 main indicators: whether sex stratification was prespecified; the proportion of female participants included; whether sex-related results were reported and whether a discussion of any or no sex-related findings was present. The authors found that inclusion of women was not linked to meaningful analyses of outcomes by sex. A bit more than half of all RCTs do not have any sort of sex-specific analyses.

There is an urgent need to move beyond the simplistic reporting of baseline characteristics, and actually achieve insights into sex-specific outcomes.

- Geller, S. E., Koch, A. R., Roesch, P., Filut, A., Hallgren, E., & Carnes, M. (2018). The More Things Change, the More They Stay the Same: A Study to Evaluate Compliance With Inclusion and Assessment of Women and Minorities in Randomized Controlled Trials. Academic Medicine: Journal of the Association of American Medical Colleges, 93(4), 630–635. https://doi.org/10.1097/ACM.0000000000002027.

This study investigates the levels of compliance in 2015 with the NIH Revitalization Act of 1993, and they compare them with the ones from 2004-2009. They employ a good number of RCTs: 782. The most relevant result is that they found no statistical change compared to previous studies, in terms of sex inclusion in RCTs.

If NIH policies do not suffice pharmaceutical R&D, should we move on to harsher journal policies?

This reading is relevant given that it provides an updated view on the state of the actual implications of the NIH policy. The main result is also interesting. It is also quite short and straightforward, although it does lack figures.

- Mazure, C. M., & Jones, D. P. (2015). Twenty years and still counting: Including women as participants and studying sex and gender in biomedical research. BMC Women's Health, 15(1), 94. https://doi.org/10.1186/s12905-015-0251-9.

This paper offers a historical perspective on the inclusion of sex and gender within drug development within the USA. The authors describe in detail the milestones in the inclusion of sex and gender within RCTs.

The most relevant aspect is that, given the failure of NIH policies to actually make a change for including sex diversity within drug development, the solution is not to wait for a cultural shift that promotes this attitude, but instead, they propose specific recommendations for change regarding the NIH, FDA, the training of scientists and clinicians, scientific publications, peer reviews and the translation and communication of research findings.

- Prakash, V. S., Mansukhani, N. A., Helenowski, I. B., Woodruff, T. K., & Kibbe, M. R. (2018). Sex Bias in Interventional Clinical Trials. Journal of Women's Health, 27(11), 1342–1348. https://doi.org/10.1089/jwh.2017.6873.

Here is a nice meta-study of the webpage ClinicalTrials.gov, where the main hypothesis is that there is not a balanced representation of both sexes within these trials. Data is from interventional Phase I, II and III from 2011 to 2015, along with numerous metadata: funding, source, purpose, etc. They gather up to a total of 1,668 studies.

Main results: There was a significant difference in the sex of the subjects included in Phase I (64.1% male/35.9% female), Phase II (48.4% male/51.6% female), and Phase III (51.0% male/49.1% female) clinical trials. Only 5% of their trials had 100% sex matching. Again, sex bias is still present despite NIH legislation.

- Ravindran, T. S., Teerawattananon, Y., Tannenbaum, C., & Vijayasingham, L. (2020). Making pharmaceutical research and regulation work for women. BMJ, 371, m3808. https://doi.org/10.1136/bmj.m3808.

This article is a good read that is concise and short. It goes over key points:

- There are still visible gaps within the integration of sex-specific outcomes in clinical trials, even though there is increasing knowledge on the differential response of both males and females, and regulatory policies.

- They propose recommendations: Stronger governance and oversight, along with commitment by researchers.

- They recommend that more women be committed to gender equality in leadership and decision-making roles in pharma research and regulation.

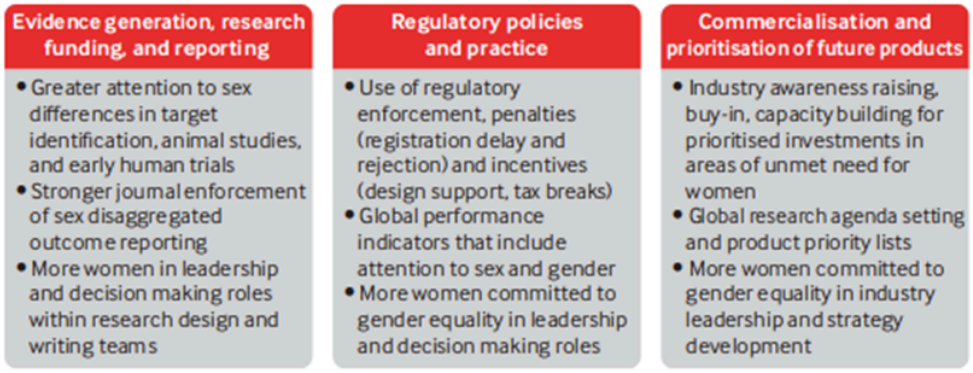

Fig 2 | Sex-gender responsive research and regulations to support women's access to appropriate medicines and health technology

- Woitowich, N. C., Beery, A., & Woodruff, T. (2020). A 10-year follow-up study of sex inclusion in the biological sciences. ELife, 9, e56344. https://doi.org/10.7554/eLife.56344

This meta-research article studies if the NIH policy that required researchers to consider sex as a biological variable had any effect in 2019. This paper is interesting because it compares their results with those of Beery and Zucker (2010), which is an article that is also included in this bibliography.

Main takeaways: Compared with Beery and Zucker (2010), although there has been an actual increase in the proportion of studies that do include both sexes, the proportion of studies that include data analysed by sex is the same.

There was a lack of rationale for single-sex studies, as well as sex-based analyses.

Authors still see that sometimes the cause of leaving female subjects outside of these studies is due to misconceptions surrounding hormonal variability.

There are still gaps in analyses and reporting of data by sex, even though sex-inclusive practices have become a bit more common.

- Zucker, I., & Beery, A. K. (2010). Males still dominate animal studies. Nature, 465(7299), 690–690. https://doi.org/10.1038/465690a.

A one-page read. It is short, but it summarises some of the previous key points mentioned: The use of male-only rodent models for some biological disciplines is widespread, and this has evident consequences on the general application of the results from these male-centred results.

- Zucker, I., & Prendergast, B. J. (2020). Sex differences in pharmacokinetics predict adverse drug reactions in women. Biology of Sex Differences, 11(1), 32. https://doi.org/10.1186/s13293-020-00308-5

This is an insightful study on the presence of a difference of effects between men and women of a given drug.

There is an interesting result: Sex-differences in pharmacodynamics and pharmacokinetics can predict the actual differential outcome or possible adverse reactions between male and female subjects. It is obvious that drugs do not interact in the same way between men and women. However, this is the only study that was found that specifically addresses this.

Proposed didactic activities

- Do a group roleplay. The setting can be for example the development of a given drug. Participants will have to take different roles (in groups of 3-4 people).

    - R&D development of the drug company
    - Clinical trial supervision
    - The pharmaceutical company
    - The end-users of the drug
    - An ethics committee overviewing the development
    - The journal / publisher of the study / the peer-reviewers of the paper

- With this, present some problematic scenarios, for example:

    - Drug X has shown to have greater adverse reactions in women after having been produced and sold in the market. Posterior experiments confirm that drug X has a completely different pharmacodynamic effect in women. The secondary effect is not really dangerous, however, in the 5% of cases, it does result in an adverse reaction that provokes some women to end up in the ICU. The pharma company states that it is not possible to re-do the whole clinical trial, and they agree to pay for damages to the hospitalised women and also argue that they had close to 50% parity in the design of the clinical trial.

- Here, each group will have to defend their position, and elucidate what would be the best possible actions they could take to improve the inclusion of the sex dimension in the general drug development workflow, if they think it is necessary.

Table 1
Recommendations for considering age and sex in drug development studies.

In vitro experiments
1. Report the genetic sex of human or animal cells lines and cultured cells
2. Compare male and female cells
3. Record the age of the donor
4. Document the growth conditions and number of passages of all cell lines and cultured cells
5. Add estrogen or testosterone to plated cells to determine effects

Animal experiments
1. Report the sex and age of the animals
2. Include both sexes in animal experiments
3. Include pregnant animals
4. Analyse results separately for male and female animals
5. Explore the possibility of sex and age differences using small stratified samples
6. Use a factorial design to independently assess the effect of sex or age
7. Consider the role of gonadal hormones across the age span
8. Pay attention to the effect of animal caging

Phase 1 and 2 human drug trials
1. Include 50% women across Phase 1 and Phase 2 trials, mass volume and bioequivalence studies
2. Adequately represent adults over the age of 75
3. Collect data on age of menarche, menopause, pregnancies and adverse pregnancy events, ovariectomy, hormonal conceptive use and hormone replacement therapy
4. Control for menstrual cycle phase when testing premenopausal, cycling women
5. Determine whether sex-specific thresholds for biomarkers are required
6. Investigate pharmacogenomic mechanisms to explain sex differences
7. Stratify samples by age and sex to detect differences in immunogenicity for the evaluation of biologics
8. Disaggregate and report results by age and sex

Phase 3 drug trials
1. Calculate sample size *a priori* to detect between or within group age and sex differences, based on substantive preliminary data
2. Employ targeted methods to recruit and retain women and older adults
3. Include pregnant women and persons with dementia
4. Collect data on age of menarche, menopause, pregnancies, ovariectomy, hormonal conceptive use and hormone replacement therapy
5. Consider adaptive clinical trial designs to determine age and sex-based dosing
6. Disaggregate and report the raw data by age and sex for all outcomes and drug harms

Post-marketing
1. Promote data-sharing and transparency
2. Disaggregate results by age and sex
3. Stratify by age
4. Analyse sex and age interactions
5. Consider changing the label recommendations for dose adjustment
6. Reverse translate observations into basic science research on new mechanisms

- The whole activity should be presented using the tables from Tannebaum and Day (2017) as a template. Each participant has to state at least some of their recommendations, and these can serve as a guide for the trainer.

- The interesting point here, is that trainees come up with the actual problems that are seen with policymaking, basic research and lack of focus on sex-dependant outcomes.
- The figure and table shown below are from an Open-Access article with a Creative Commons CC-BY license: © 2017 The Authors. Published by Elsevier Ltd.

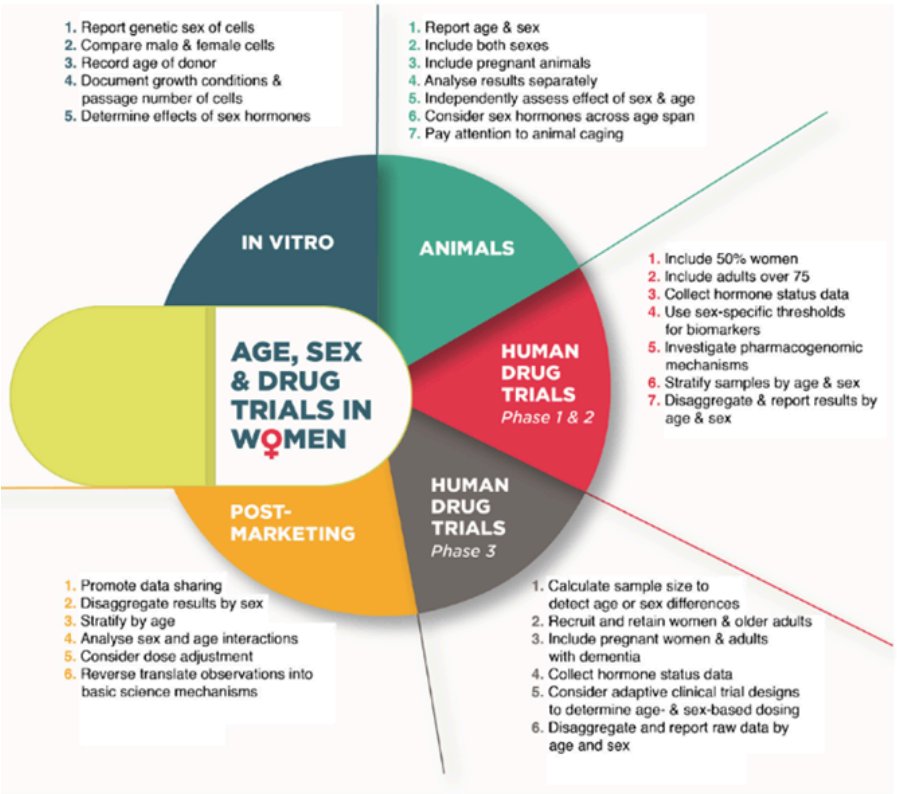

Fig. 1. Cycle of age and sex-specific translational and post-translational drug development.

Takeaways

- The lack of gender diversity in pharmaceutical research and clinical trials has led to suboptimal healthcare for minorities and female individuals.
- The historically disproportionate use of male animal models in clinical trials has contributed to the gender bias and limited understanding of drug dynamics between males and females.
- Despite efforts to address gender bias through legislation and policies, significant disparities persist in all phases of clinical trials, necessitating further actions for adequate representation and understanding of drug effects across genders and populations.

INTEGRATING THE SEX AND GENDER DIMENSION INTO SOCIAL IMPACT OF TECHNOLOGY

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Introduction

The failure to consider sex and gender dimensions when developing technologies, medical technologies in particular, often leads to disparate negative impacts of these technologies, most often on those deviating from the "typical white man". This is particularly relevant given the actual context, where technology shapes our daily lives, ranging from our online behaviour (Postmes & Spears, 2002) to the impact of cutting-edge medical technologies.

The below resources and activities discuss these issues as well as how we can go about developing unbiased technologies that have a fair, positive impact on the whole diversity of end-users.

Selected resources

- Postmes, T., & Spears, R. (2002). Behavior Online: Does Anonymous Computer Communication Reduce Gender Inequality? Personality and Social Psychology Bulletin, 28(8), 1073-1083. doi:10.1177/01461672022811006

Innovations in technology inspire the belief that gender inequality won't be significant in the virtual world because the properties of anonymity and isolation are thought to reduce the restraints that we feel others may impose on us. However, the study found that this was not true. It found that online interactions did not lead to equalisation in participation, and that gender differences in dominance were most accentuated when group members were unable to make distinctions between members and identify the gender.

- Schiebinger, L. (2014). Gendered innovations: harnessing the creative power of sex and gender analysis to discover new ideas and develop new technologies. Triple Helix, 1(1), 9. doi:10.1186/s40604-014-0009-7.

This article discusses "*gendered innovation*" and the importance that considering sex and gender within research can lead to new and improved innovations. It gives examples of how often once sex and gender are taken into consideration, knowledge about a topic significantly increases. More specifically, it also discusses how within the medical field, medical technologies used for diagnostic purposes may more often misdiagnose or fail to diagnose women versus men (angiogram example, see Figure 2 from the reference article) most likely due to the fact that they were designed based on clinical studies that did not include women and thus may have missed symptoms that are unique to women and not men.

This is a good example of how technologies themselves can perform differently based on the sex of the patient or have greater effectiveness/success on one sex versus the other due to biases present when creating the technology.

The article emphasises incorporating sex and gender from the beginning and becoming proactive instead of reactive.

- Gilles, K. F.-J., Charlotte. (2012). When Technology and Tradition Collide: From Gender Bias to Sex Selection. Retrieved from https://www.prb.org/wp-content/uploads/2021/02/10152012-gender-bias-sex-selection.pdf.

This article discusses prenatal sex selection and how the technology invented to determine the sex of a baby before it is born has had a differing impact on society depending on one's sex (or the sex of the baby). Due to deep-seated societal biases favouring males, babies born of the female sex who were identified as so before birth by this technology are more likely "to go missing" than babies who were identified as male, or the birth ratios in certain places are skewed in favour of male babies because pregnancies with female babies are more likely to be terminated after the sex of the baby is determined.

This is a good example of how the performance of the technology itself is not impacted by or differs based on sex, but its application in the real world reveals the underlying biases that exist in our society today.

- Gendered patterns in use of new technologies. (2023). Retrieved from https://eige.europa.eu/publications-resources/toolkits-guides/gender-equality-index-2020-report/gendered-patterns-use-new-technologies?language_content_entity=en.

This article gives a general overview on how technology use differs between men and women (note that it says it is looking at gender but just mentions binary men versus women). It shows that men often are more likely to use, have greater access to, and have greater confidence in technologies. But, when it comes to social media, women are more likely to share content.

- Tannenbaum, C., Ellis, R. P., Eyssel, F., Zou, J., & Schiebinger, L. (2019). Sex and gender analysis improves science and engineering. Nature, 575(7781), 137-146. doi:10.1038/s41586-019-1657-6.

This article discusses how including sex and gender dimensions in research will improve reproducibility, applicability of results, and experimental efficiency by reducing biases. It also provides a roadmap for the best ways to analyse sex and gender across scientific disciplines.

Proposed didactic activities

- Building on a health case study from Stanford's *Gendered Innovations* referring to Medical Technology, create questions that allow for a discussion that highlights the following key points:

  - The need for a non-biased, representative dataset in the first place.
  - The importance of having a diverse team developing these technologies.
  - The importance of testing the effectiveness of these technologies on a diverse group of patients
  - How in some cases, sex or gender-specific technologies may need to be developed.

- Some examples of said questions could be:

  - As we can see, medical technologies often disproportionately harm females and others who do not fit the "typical male" profile. In the above examples, what were some of the specific reasons for the poor performance of these medical technologies?
  - As highlighted in the section about correcting dataset bias, unrepresentative datasets can lead to poor-performing technologies, which can lead to further unrepresentative datasets or lack of knowledge. What are actions we can take in order to break this cycle? How can we ensure that the data we are working with and the data we are gathering is unbiased?
  - It is very clear that considering sex and gender in the development of medical technologies is very important. Therefore, are there cases where creating separate sex-specific or gender-specific technologies is beneficial? Are there cases where it is not (This can be nicely linked with the following GI case study)

- Building on a health case study from Stanford's *Gendered Innovations* referring to knee prosthetics, create a discussion around the following points.

  - As we know, sex and gender are important to consider when developing medical technologies. But, relating to the above example, what are the potential risks of doing so? Discuss these risks and what we can do to mitigate them while still making sure sex and gender are properly considered.

- Reading & commenting: Read the source in the above bibliography called "When Technology and Tradition Collide: From Gender Bias to Sex Selection" up until the section labelled "Promising Approaches".

  - How is this example of the impact of technologies on sex and gender different from the ones discussed above?
  - Is the technology itself performing in a biased way?
  - What are the important takeaways about what we should consider when developing new technologies?

Takeaways

- Technologies are often tailored to men, sometimes unintentionally, and this has a negative impact on women's health outcomes.
- Sex and gender must be considered in all steps of the development process of new technologies, such as who is represented in the data, we are basing our development on, who are the developers, and who are we testing the developed technologies on.
- It is important to consider the real-world impact of technologies being created, more specifically how the impact may differ depending on sex and gender.

INTEGRATING THE SEX AND GENDER DIMENSION INTO TOOLS FOR BIAS MITIGATION

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Introduction

Data-driven algorithmic systems, as of today, are widespread within the biomedicine field. They play a key role in determining patterns within high-dimensional biological data. However, there has been an effort to make said systems more trustworthy, transparent, and unbiased. The reason is that biased systems result in model outputs that are not reliable and can therefore lead to incorrect decisions. Given the many points within the AI workflow where biases can appear, there are many options and tools for unbiasing these algorithms.

Biases can be tackled at a) the data pre-processing step, b) by using inherently "transparent" algorithms that have been built to be explainable or c) after obtaining the output of the algorithm, in a post-hoc manner.

There are some well-known datasets that have been employed to first prove the existence of such biases and prove that such biases can have actual consequences on real-life decisions. An example is the COMPAS (Correctional Offender Management Profiling for Alternative Sanctions) Recidivism dataset, used to assess a convicted criminal's likelihood of reoffending, and used as a use-case for bias against African American offenders. Note that most of the common datasets used to showcase these biases do not specifically tackle the sex and gender dimension, or the biomedical field. Nevertheless, the methodologies, and tools can be equally applied to a certain dataset that is gender-biased and related to any biological data.

Selected resources

- Bellamy, R. K. E., Dey, K., Hind, M., Hoffman, S. C., Houde, S., Kannan, K., . . . Zhang, Y. (2019). AI Fairness 360: An extensible toolkit for detecting and mitigating algorithmic bias. IBM Journal of Research and Development, 63(4/5), 4:1-4:15. doi:10.1147/JRD.2019.2942287 A technical paper that explains the IBM Toolkit, written in Python. Includes information on the different fairness metrics for both datasets and models. Also explains the algorithms employed to mitigate these biases.

The figure below is a good overview on the different steps within the AI pipeline where this fairness could be applied.

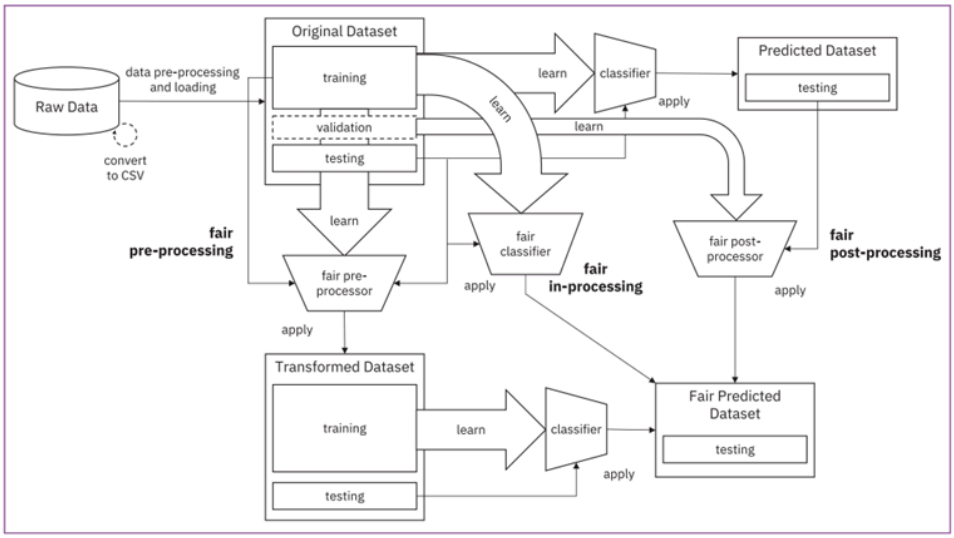

Figure 1

Fairness pipeline. An example instantiation of this generic pipeline consists of loading data into a dataset object, transforming it into a fairer dataset using a fair pre-processing algorithm, learning a classifier from this transformed dataset, and obtaining predictions from this classifier. Metrics can be calculated on the original, transformed, and predicted datasets as well as between the transformed and predicted datasets. Many other instantiations are also possible.

The paper is not open-access, and it is technical in some parts. However, the main relevant idea is the different metrics to employ, which are agnostic to the type of bias, therefore they are also extremely useful for sex and gender biases.

- Norori, N., Hu, Q., Aellen, F. M., Faraci, F. D., & Tzovara, A. (2021). Addressing bias in big data and AI for health care: A call for open science. Patterns (N Y), 2(10), 100347 https://doi.org/10.1016/j.patter.2021.100347

This is an introductory paper to biases in AI, and their relevance within the biomedical field, addressing current issues and possible future steps. The authors define three axes for biases in the medical field: data-driven, algorithmic, and human. It is a light read, given that it is not technical at all.

Main takeaway: It puts a focus on open science, and how a more fair and accessible scientific ecosystem is closely intertwined with the possibility of addressing AI biases (See Figure 2 of the paper).

There are three main specific recommendations that they propose, and, for each one, a series of concrete examples are also given.

- Participant-centred development of AI algorithms and participatory science;
- Responsible data sharing and inclusive data standards to support interoperability;
- Code sharing, including sharing of AI algorithms that can synthesise underrepresented data to address bias.

It might not be directly related to a specific tool, but it offers a good set of recommendations on how to actually address sex and gender (and diversity in general) within these AI tools. In order to address sex and gender in AI algorithms, there must be prior work in order to create the proper scientific, social and technical setting to do so. This paper follows this direction, raising awareness and proposing possible solutions, making it useful for this topic.

- Chakraborty, J., Majumder, S., & Menzies, T. (2021). Bias in machine learning software: why? How? What to do? Paper presented at the Proceedings of the 29th ACM Joint Meeting on European Software Engineering Conference and Symposium on the Foundations of Software Engineering, Athens, Greece. https://doi.org/10.1145/3468264.3468537.

The authors claim that this is "one of the largest studies on bias mitigation yet presented in the literature."

Main point: Study what are the actual root causes of bias. They hypothesise that it is located in the steps *prior to* the actual use of the model, the prior decisions that generated the training data, how the data is collected, and the labels assigned to those samples. Therefore, they focus on data imbalance between sensitive classes (e.g., sex), as this will affect the whole AI workflow downstream.

They develop an algorithm, "Fair-SMOTE", that specifically rebalances these relevant attributes.

The results section nicely presents this information in research question blocks, the most relevant info can be quickly summarised from here.

- Wiśniewski, J. B., Przemysław (2022). fairmodels: A Flexible Tool For Bias Detection, Visualization, And Mitigation. The R Journal, 14/1, 227 - 243. doi:10.32614/RJ-2022-019.

This journal article outlines a model-agnostic approach to bias detection, visualisation, and mitigation. The implemented set of functions and fairness metrics enables model fairness validation from different perspectives.

It delivers a series of methods for bias mitigation that aim to diminish the discrimination in the model. It allows for comparisons between multiple models. They include 12 fairness metrics, as well as bias mitigation within the data pre-processing and model post-processing steps.

To note: The set of different plots for visualising this bias that the package includes is a valuable implementation and shows that different types of variables might require different representations of their data to actually detect this bias.

Interesting question: What is a considerable amount of bias? For this, they follow the "four-fifths rule". Although with some caveats, they assure that it is a good rule of thumb.

  - They provide an example workflow for bias mitigation within a widely used German Credit dataset.
  - Note that this is a pre-print, it has not been peer-reviewed yet.

- Orphanou, K., Otterbacher, J., Kleanthous, S., Batsuren, K., Giunchiglia, F., Bogina, V., . . . Kuflik, T. (2022). Mitigating Bias in Algorithmic Systems—A Fish-eye View. ACM Computing Surveys, 55(5), 1-37. doi:10.1145/3527152.

This is an extremely extensive review that focuses on four different research domains: Machine Learning, Information Retrieval, Recommender Systems and Human-Computer Interaction. They compare different approaches to bias mitigation in all of them.

It includes a remarkable bibliography. For each specific field, the authors have outlined the solutions proposed for mitigating bias and measuring fairness.

They highlight the different notions of fairness that are employed across different fields: Statistical measures; Similarity-based measures and causal reasoning. Section 5.5. further develops this point.

Main takeaways:

- Although there are many common, shared and formalised definitions of fairness employed across, there is an issue surrounding perceived fairness. This is subjective, specific to the user of the algorithm and presents a much more complex (but interesting!) debate. For this specific topic, the authors claim that ensuring transparent, explainable systems can be useful for improving the user's perception of the fairness of a given system.

- There are two main types of attributes that are the source of bias: Attributes that describe the world and attributes that describe information. XAI manages those referred to information, and fairness metrics tackle those variables describing the "social" dimension.

- They focus on the fact that the work done on bias mitigation and fairness implementation has to take into account **multiple stakeholders**, including the developers, end-users, observers and even indirect users.

This is a good paper, although a bit too extensive, one can avoid sections not related to Machine Learning, as well as sections that go too deep into Explainable AI (XAI) (Section 6. Explainability Management).

Table 1. Key Publication Venues Reviewed Per Domain

Domain	Publication Venues Reviewed	# Papers
Machine Learning/AI	AAAI, IJCAI, KDD, SIGKDD, CIDM, ICML, AIES, NIPS, MLSP, ACM Data Mining and Knowledge Discovery Journal	106
Information Retrieval	ACM SIGIR, ACM CIKM, ACM WWW, TOIS, JASIS, IR Journal, (AAAI ICWSM)	68
Recommender Systems	ACM RecSys, AAAI ICWSM, UMUAI, ArXive (ACM CSCW, ACM CIKM, ACM FAccT (formerly FAT*))	46
Human Computer Interaction	ACM CHI, ACM CSCW, ACM CHI Journal, CSCW Journal Journal of Behaviour and Information Technology	34
Other	AAAI HCOMP, ACM FAccT, ICDM,VLDB	57

Demos for bias assessment

We collected a series of popular and ready-to-use online tools for a first-contact with debiasing algorithms.

- IBM Fairness 360 (Bellamy et al., 2019).

The Web demo is available here. On this website, IBM allows testing for different debiasing methodologies on three common datasets. It also shows different debiasing methods for various steps within the ML workflow, from data pre-processing to fair algorithms and post-hoc bias mitigation. They also explain different fairness metrics that can be employed.

- Aequitas Bias and Fairness Audit Toolkit.

This webtool is an *"[...] open-source bias audit toolkit for ML developers, analysts, and policymakers to audit machine learning models for discrimination and bias, and make informed and equitable decisions around developing and deploying predictive risk-assessment tools*". By default, the COMPAS dataset is given as a use-case, although it allows for other datasets.

- Microsoft Fairlearn.

Developed by Microsoft, this website is an *"open-source, community-driven project to help data scientists improve fairness of AI systems"*. The website is focused on how to think about fairness as sociotechnical, and how to use Fairlearn's metrics and algorithms while considering the AI system's broader societal context.

- What-If Tool (WIT)

Proposed didactic activities

- The demos can be of great help. Most of them, if not all, are actually online, and can be used to do a small demonstration.

- The one from IBM, the AI Fairness 360 includes a really comprehensive, step-by-step guide to explore with 3 different datasets and different debiasing methods, along with nice comparative plots.

- The pro is that it does not require anything but the actual webpage, so no Jupyter notebooks or the need to download something specific. It is really accessible for the attendees.

- The con is that it is difficult to make it engaging, as attendees might lose focus on what is being explained while trying to follow the tutorial themselves. In order to avoid this, we propose the following activities to highlight the main points of this topic:

- Asking questions *before* using the dataset. If we have a dataset on income prediction: What kind of biases could we have here? What would be the sensitive attributes? What attributes do they assume are most important for this classification task? What would be a *fair* way to distribute the individuals within the dataset?

- Asking general questions about abstract concepts, such as fairness and bias. What do we consider to be fair? What is bias? Is there a positive bias?

    - This is positive in the sense that forces attendees to focus on these concepts.
    - The idea is that after some discussion, some definitions have to be presented by the trainers, in order to make it clear.

- Asking where the attendees think the effect of bias is most important within the workflow, if in the pre-processing step, while building the model or after having obtained the output of the model. This can be interesting to explore also before running an example of a debiasing tool (e.g., IBM AIF360 allows debiasing in all these three steps). The actual answer is that *it depends* (e.g., on the dataset, the task, who is using it), but it is a useful exercise.

Takeaways

- Biomedicine heavily relies on data-driven algorithms for pattern analysis in biological data.
- Efforts are being made to improve trustworthiness, transparency, and unbiasedness of algorithmic systems in biomedicine to prevent incorrect decisions.
- Various stages, such as data pre-processing, algorithm selection, and post-hoc methods, offer options and tools to mitigate biases in biomedicine and other fields dealing with biological data.

Implementation guidelines

IMPLEMENTATION GUIDELINES

SARAH MORGAN

EATRIS

Introduction

These guidelines aim to offer practical insights for trainers in the life sciences on effectively integrating the sex and gender dimension into their training. Effective communication is emphasised, including providing comprehensive information about the course in advance, setting the learning environment, establishing codes of conduct, and ensuring a common understanding of terms and course objectives. When leading interactive or discussion sessions, clarity of purpose, rules of engagement, monitoring of activities, and effectively concluding the session are highlighted. The guidelines also address assessing and evaluating learning, considering the purpose and type of assessment, the various assessment methods, marking, and providing feedback. For further exploration, additional reading on this topic is recommended.

Communication

Guidance	Explanation	Additional notes
Communicating details about the course ahead of the event	• Managing course expectations from the first time a potential student / trainee finds your course and starts to read the description. • The course description needs to be clear, providing a comprehensive overview of the course aims and anticipated outcomes. It should be written in language which is free of jargon and colloquialisms e.g., if in English, able to be understood by a non-native speaker. • The language used in course descriptions should be free of stereotypes (e.g., when providing audience examples) and use inclusive language at all times (they / them rather than she / he).	Some examples of course descriptions: EMBL-EBI Structural bioinformatics | EMBL-EBI Training EATRIS TMex - Translational Medicine Explained 5 day winter school 2023 - EATRIS

Setting your learning environment at the start of the course	• As course lead or course tutor, your role is to make the learning environment comfortable for all to learn. • Firstly look at the room layout – is it compatible with the type of session you wish to run? Some rooms can be moved around, if not, think about how you can use the room to the best advantage. • Set your expectations of how the course / session will run from the outset. • Make it clear how you want interactions to occur e.g., if you are happy to have questions asked throughout, say so – if you would prefer to get people through a particular piece first then have a big open forum, let them know. • If there are elements of group work / moving around groups and the room, again let them know at the start of the session. • Show them you are approachable and invite them to talk to you about any potential issues at an early stage in the session. • Set the tone for how you expect your trainees / students to work together; showing mutual respect for all in their approach to each other. • The "live" environment becomes important as soon as students / trainees join on day 1 – if you are providing nametags, consider including the option for pronouns, so people can be addressed in the way they feel most comfortable.	Put yourself in your trainees' / students' shoes – be empathetic to how they may feel, especially if they are new to a subject or have not studied in a while. Think about how you can make them all feel more confident in their learning.

Codes of conduct	• Many training providers / educational establishments have a code of conduct that they ask all their trainees / students to sign up to upon accepting a place in the course. • If one has not been created, then you can set one ahead of the course. • An activity at the start of the course could be to define your code of conduct with the group; this might help when looking at definitions. If you create one, make sure everyone has access to it, including tutors / trainers / teachers that will be involved later in the course.	ELIXIR code of conduct for events: ELIXIR Hub Code of Conduct for events | ELIXIR (elixir-europe.org) EMBL events code of conduct Code of Conduct – Course and Conference Office (embl.org)
Common understanding of terms / definitions to be used and the aims of the course	• Individual understanding of terms and their definitions in the discussion of sex and gender can vary greatly, with some taking a more nuanced approach, whilst with others everything is black and white. • Time may be required to ensure that everyone is approaching the terms in the same way so there is a shared understanding of the terms and how they are to be /can be used. • Knowing which terms are appropriate to use in which scenarios / discussions can help empower people to take a more active part in activities. • A glossary of terms ahead of a course may help in setting a shared understanding from the beginning.	UNICEF glossary of terms and concepts for gender equality Gender equality: GLOSSARY OF TERMS AND CONCEPTS (unicef.org)

Leading interactive / discussion sessions

Clear purpose	• Discussions and interactive sessions can be fun elements of learning, providing individuals with a different way to gain new knowledge and skills with a practical basis. • Fun alone is not a good reason to include such sessions though – as with all teaching activities, there needs to be a clear purpose from the start. • This purpose needs to be clear to you as the trainer / teacher and should be clear to the students at an appropriate time (sometimes you may want them to start the discussion and through that process the learning point will become clear). • A clear purpose will enable you to set up the session appropriately, including the provision of necessary resources; and also to steer the discussion / session, if needed, due to straying off into "unhelpful" tangents. (Sometimes tangential discussion can be useful – so it is also good to know if it moves into territory that can provide useful learning.)	As for all teaching sessions, set learning outcomes (LOs) so you know what you are setting out to achieve. For LO advice, see the ELIXIR TtT handbook. ELIXIR-EXCELERATE-TtT/TtT_session_1.md at master · TrainTheTrainer/ELIXIR-EXCELERATE-TtT · GitHub

Rules of engagement	• Clear rules on how the session will run should be set at the start; this ensures everyone has the opportunity to participate and can also be used as a way to make interaction more comfortable / empower people to participate. • For some, group discussions can be worrying; people may not feel confident coming forward with their ideas and opinions. Acknowledge this, but try to encourage all trainees / students to join in. • Think about group size (3-5 is often an optimal size for all to be able to participate) and consider how groups will be selected – do you allow people to self-select or do you have some way of choosing (e.g., give everyone a number). Both ways have their merits and downsides.	An interesting (brief) article on setting your ground rules as a trainer: Ground Rules for Training Adults in the Classroom | DataDrivenInvestor

Monitoring of activity / crowd control	• Keep an eye on your teaching group throughout the session
	• Walk around the group and find out how things are progressing, keep a look out for:
	  ◦ Groups that are very noisy. (Are they still happy working together? Have they gone on a tangent?)
	  ◦ Groups that have gone quiet. (Have they run out of things to say or are they taking time to reflect individually?)
	  ◦ Individuals who are dominating their group discussion. (Do you need to defuse and reduce their domination to give others an opportunity to speak?)
	  ◦ Individuals who are very quiet and do not appear to be engaging. (Approach their group and ask them some questions in a non-threatening manner.)
	• Encourage a balanced approach to discussion and to who chooses which jobs; groups usually need some form of a leader to ensure work happens, but someone taking the lead should not dominate all the work that is done.
		Advice on facilitating group discussion:
		Tips on Facilitating Effective Group Discussions | Sheridan Center | Brown University
		
		This includes some useful commentary on potential problems that can arise during discussions and strategies for working with them.

Drawing things to a close	• Take the lead again on timing – remind trainees and students what their final output should be and how long they have left. • Be flexible with final time and outputs if possible – e.g., if trainees / students feel they have been unable to complete the task or require more time to do so, try to ensure this is not seen as a "failure" in task.	

Final outcomes & outputs (and linking to other activities)	• How are you going to bring your discussion or session to an end? • What are the final outputs you expect your trainees / students to produce and what is the final "take-home" message? • How will you link this to other learning through the course? • Students and trainees often feel "let-down" if they have spent time on an activity without a clear end or clear output – even if time is running away from you, make sure to bring the activity to a close and provide some final thoughts. If time allows you could also re-visit the discussion at a later point in the course.	

Assessing / evaluating learning

Consider the purpose and aim of the assessment	• Who is the assessment for? You, the trainees / students or both? • Why are you assessing, and what do you hope to learn? • Assessing at the start of a course can give an idea of knowledge / skill levels at that point. • Assessing at the end provides everyone with the final evaluation of what they have gained during the week. (It is important to recognise that in a short course environment, trainees have not had much opportunity to practice / apply their newfound skills and knowledge much at that point). • Assessing during a course allows for an interim view of knowledge and skills acquisition and may allow for remedial work if required or enable a course to progress quicker.	

Assessment types: Formative or summative?	• Summative – the assessment has a marking scheme or rubric attached to the final score or grade that a student or trainee is provided with at the end. This approach is often applied in educational courses which lead to a formal qualification, or in some CPD courses where a number of credits needs to be gained on an annual basis. • Formative – no final score or grade is given, but feedback is provided on goals achieved, giving an indication of the learning achieved / knowledge and skills acquired. This form of assessment is often applied in short courses where trainees are gaining "just-in-time" skills and knowledge.	
Assessment types: Formal or Informal?	• Formal and informal assessments again relate to the way in which the assessment is given and how results are fed back to students & trainees. • Similar methods of assessment can be applied for both types, but the context in which they are run differentiates them. • Formal types are those which provide a check on achievement at a particular point in the learning e.g., a group challenge on the last day of a practical bioinformatics course, where trainees bring together knowledge and skills gained during the course and apply it all to a set challenge. Both they and their tutors are then able to see the final progress made. • Informal types are those assessments that are used to check how learning is progressing e.g., quizzes, puzzles, practical activities. These can be applied at any time during a course and may actually not feel like assessments to participants, but they are a useful tool for trainers to see how their learners are progressing and can help consolidate learning for trainees / students.	

Assessment methods	• Assessment methods are many and varied, and it is worth talking to other trainers / teachers to find out the kind of methods they use. Some examples are: • Informal formative: Quizzes, quick show of hands, post-it note sessions, brainstorms – all great ways to assess knowledge at the start and check learning progress during a course. • Formal formative: practical sessions (Do students achieve the end goal?), group / individual challenges, reflection piece • Formal summative: assignments with a set rubric / mark scheme, journal reports, reflection piece. • This list is of course not exhaustive, and there are many creative ways in which you can assess learning!	For quick (but interesting) ways of adding informal evaluations, try using tools such as Mentimeter or Kahoot in your teaching.
Marking	• If an assessment is summative, then a clear marking scheme or rubric should be written at the same time as the assessment is set out. This should be clear to markers (whether they wrote this or not) and should be clear to trainees. • Having a clear marking scheme should reduce / remove bias in marking, but some flexibility may be needed if students are able to bring in a number of themes / paths for their assessment. • Where possible, marking should also be anonymous so that markers do not know whose work they are marking – again ensuring bias is removed.	

Feedback	• Ensure feedback is clear and unambiguous – written where possible to provide a record that trainees / students can return to; or if verbal, again provided as a recording. • As with communication, be clear in use of language, steer away from too much jargon or colloquialisms. • Encourage trainees / students to seek clarification if required; or discuss ways in which they can apply feedback when they next use their new skills / knowledge.	

Recommended resources

Ten simple rules for unbiased teaching | PLOS Computational Biology – a fantastic overview of things to think about, covers a number of the themes mentioned above. Well worth a read!

Ten simple rules for leveraging virtual interaction to build higher-level learning into bioinformatics short courses | PLOS Computational Biology Though focused on virtual learning, there is some useful advice here for managing group dynamics, introductions and ice breakers.

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