Predictive Model to Estimate Baseline Serum Estradiol Concentration in Female Laboratory Mice

Estradiol: Unraveling Complexities in Hormonal Health

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By
Mikayla Jackson

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Technical Team Members:
Samiya Syeda, Ramya Tangrila, Khatiana Perez, Gregory Lawrence

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

Dr. MC Forelle, Department of Engineering and Society

Dr. Sylvia Blemker, Department of Biomedical Engineering

Introduction

Estradiol, a crucial member of the estrogenic compound family, holds significant importance within human biology and medicine. It plays a crucial role in regulating the female reproductive system, including the development of secondary sexual characteristics like breast growth and the maintenance of a healthy menstrual cycle. Its relevance extends across various areas of reproductive health, development, and overall physiological and psychological well-being. During a woman's menstrual cycle, its levels fluctuate significantly, peaking just before ovulation to prepare the body for potential pregnancy. Men produce estradiol in smaller quantities, primarily through the conversion of testosterone. Estradiol has far-reaching effects throughout the body, influencing bone health by promoting calcium absorption and reducing osteoporosis risk. Maintaining healthy estradiol levels not only affects cardiovascular health by promoting the relaxation of blood vessels but also by helping to maintain healthy cholesterol levels, thereby contributing to lower blood pressure. Moreover, estradiol plays a crucial role in regulating mood and brain function, which may explain some of the emotional and cognitive changes during menopause when estradiol levels decline (Dorofeev, 2022; Seifert-Klauss & Prior, 2010; Stillwell, 2010).

Previous research examining estradiol is outdated and predominantly focused on male mice (Levy et al., 2023). Female mice were assumed to cause more variable results due to their hormones and, thus, disrupt data results. Researchers also believed that the requirements regarding the use of females would hamper investigations because of a need for increased sample sizes, and increased costs. These assumptions have been proven false, highlighting the existence of a research bias that has hindered a comprehensive understanding of estradiol dynamics in female (Beery, 2018). As mentioned previously, understanding estradiol’s significance is

fundamental, and the use of female mice for experiments involving estradiol is necessary for accurately determining its serum concentrations and the estrous cycle stages. Current methodologies, particularly in predicting estradiol concentrations and discerning cycle stages, are labor-intensive, time-consuming, and require substantial lab equipment usage. Such inadequacies may lead to inefficient research practices and delay essential discoveries in the field of women's health and hormonal therapy. To counteract these challenges, an initiative is necessary to streamline and enhance the efficiency of research practices by eliminating unnecessary waiting times in lab procedures and minimizing the extensive use of equipment. Accurately determining the baseline levels of estradiol in female mice and developing a reliable predictive model for estradiol concentrations can significantly enhance the efficiency of research efforts.

In my technical project, I will be focusing on creating a predictive model for determining estradiol concentrations and the estrous cycle stages in female mice, intending to streamline and enhance efficiency in estradiol research, thereby contributing to the advancement of women's health studies. In my STS project, I will be focusing on the socio-cultural impact of hormonal health technologies, investigating the complex interplay between patient demands, regulatory influences, and societal norms in shaping the reception and resistance to these technologies.

Technical Project

In the medical field, the significance of estradiol extends to hormone replacement therapy (HRT) for women experiencing menopausal symptoms or those who have surgically removed the ovaries. HRT can alleviate symptoms such as hot flashes, vaginal dryness, and mood swings. However, using it judiciously is vital as it carries some risks. Understanding estradiol and its functions is essential for promoting health and addressing various medical conditions in both men and women (Mandal, 2023).

Our project aims to determine the baseline estradiol concentration in female mice and create a predictive model for the concentrations. The research question I seek to answer is: How can the creation of a predictive and experimental model for determining estradiol concentrations in female mice effectively streamline and optimize research methodologies within women's health studies? This will create a precise concentration predictive model and develop an accurate tool for determining the estrous cycle stage using vaginal cytology. The predictive model will have both the original data and the model's output. We will compare both using statistical tests to identify how similar the model is. The data output will contain accuracy, sensitivity, and specificity statistics to interpret the model and confirm whether it works. We will include additional statistical tests in the code and output, but we will not display them on the graph.

To improve the success rate of producing timed pregnant or pseudopregnant mice, we aim to identify the estrous cycle in mice through several techniques. Enhancing this efficiency involves identifying mice in proestrus or estrus. Researchers have developed an identification tool (Figure 1) to assist with this process, which is essential for the vaginal cytology method. The recommended approach for identifying parts of the estrous cycle is the vaginal cytology method, and we will use it along with the estrous cycle identification tool for accurate identification of all stages. The estrous cycle lasts 4-5 days and undergoes four stages - proestrus, estrus, metestrus, and diestrus. The absence, presence, or proportion of 4 basic cell types and the cell density and arrangement of the cells on the slide define these stages (Byers et al., 2012).

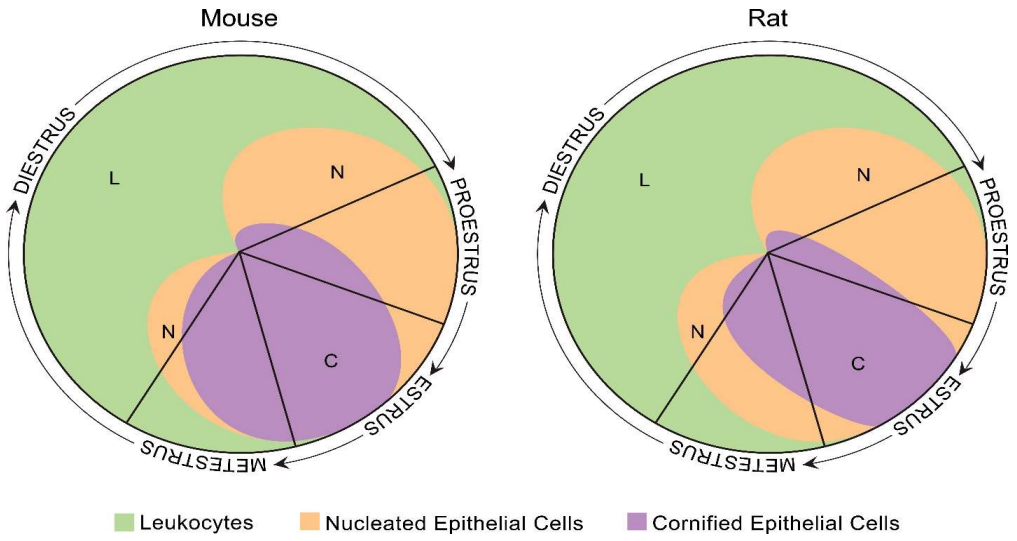

Figure 1: Identification Tool *(Byers et al., 2012)*

Researchers typically collect samples for the cytological evaluation by vaginal lavage, and this is preferred, as it yields a higher cellularity sample. After collecting the sample, we place a small drop evenly on the slide in a thin layer (smear) and allow it to air-dry. Romanowsky-type stains are popularly utilized cytological stains for identifying different cell types and are recommended for staining vaginal smears due to their excellent coloration properties. Studies have shown that Romanowsky-type stains (Giemsa, Wright, and Leishman stains) produced the best results during the first and second evaluations and had the best durability among the six stains under the study with cytology like earlier studies. Therefore, we chose this stain for the project. One general approach to staging vaginal smears is to first assess for the presence of neutrophils. If neutrophils are a dominant feature or consistently observed, the stage is either metestrus or diestrus. If neutrophils are rarely absent, the stage is either proestrus or estrus (Ani et al., 2021).

The process entails conducting routine vaginal smears, staining them, and examining them under a microscope to discern various cell types and their respective ratios, which serve as valuable indicators of the current phase of the estrous cycle. We will quantify the estradiol

concentration in mice by implementing the E2 ELISA technique. This method involves collecting blood samples from the mice and analyzing the estradiol concentration. We will ascertain the precise amount of blood required for analysis and employ appropriate blood collection techniques (Cora et al., 2015).

The predictive model aims to use data obtained from animal experimentation to improve our understanding of physiological processes. The dataset provided for data input will consist of estradiol concentration data, along with information on the mouse's respective cycle and collection day. The data output will include the predicted hormone concentration [E2] and the stages, solely based on the estrous stage. We will use a Lasso Regression Model to estimate the relationship between variables and make predictions. The primary goal of LASSO regression is to find a balance between model simplicity and accuracy. It achieves this by adding a penalty term to the traditional linear regression model, encouraging sparse solutions where some coefficients will be zero(Freijeiro-Gonzalez et al., 2021). We will use Python as the programming language and have 40-50 days of data.

The code will import the package for lasso regression and dataset, then standardize and clean up the data if needed. We will then select predictors (estrous stage, date, everything but target) and target variable (concentration). We will calculate RMSE and get the model's coefficients to see which are more critical in predicting concentration. We will also print out the graph of the model and plot the original data over it. The data output will contain statistics such as accuracy, sensitivity, and specificity to interpret the model and to confirm if the model is working. We will include additional statistical tests in the code and output, but they will not be on the graph. Our group expects that the project's predictive model and experimental aspect will

have similar outcomes. If this doesn't occur, our predictive model must be adjusted to be accurate according to mice anatomy.

STS Project

Understanding the baseline concentration of estradiol in blood serum is not only a biological and medical concern but also a matter influenced by social and political factors. These factors, including healthcare access, gender equity, and cultural attitudes, can impact an individual's ability to access information and services related to hormone levels. Furthermore, broader issues such as reproductive rights, stigmatization, and research funding, also intersect with the scientific understanding of estradiol concentrations within societal and political dynamics. Also, it is vital to consider cultural and societal attitudes toward managing estradiol levels since they can affect fertility, menstrual cycles, and pregnancy. Therefore, comprehending estradiol during specific parts of the estrous cycle is crucial to informing the public and improving decision-making about hormonal health policies.

In the past, hormone-related issues were poorly understood, which led to problematic medical practices and a history of controversies over hormone replacement therapy. This is an essential aspect of estradiol and its history within the scientific community. Given the complex social, cultural, and historical aspects surrounding estradiol, my research aims to answer the following question: "**How have previous technological advancements in the field of hormonal health and diagnostics been received by the public and medical community?**" I will explore the dynamics of the social construct of technology, sociocultural factors, and ethical implications and policy influences in hormonal health technologies.

The dynamic interplay between sociocultural dimensions and hormonal health technologies, as analyzed through the Social Construction of Technology (SCOT) framework,

reveals the diverse ways cultural norms, societal expectations, and gender identities influence the acceptance and resistance of these medical interventions. The decline in estrogen therapy in the 1970s was partly due to changing cultural attitudes towards health and risk, which was fueled by concerns about increased cancer risks (Kohn et al., 2019). Different cultural and societal groups may interpret the purpose, risks, and benefits of hormonal health technologies in different ways, which can lead to shifts in technology adoption. Additionally, gender identities also play a crucial role in the acceptance of hormonal health technologies. For instance, the use of estrogen therapy in transgender women is based on recommendations for post-menopausal women, highlighting the intersection of gender identity and medical technologies. The SCOT framework can be applied to understand the acceptance and resistance of hormonal health technologies. This framework emphasizes the relationship between sociocultural dimensions and technological adoption, highlighting the role of diverse social groups in shaping perceptions of hormonal health technologies (Wiebe, 2015). In understanding the nature of technological development, SCOT provides valuable insights into how the shaping of perceptions by different social groups plays a pivotal role in the adoption and interpretation of hormonal health technologies.

The acceptance and resistance to hormonal health technologies can also be attributed to public perceptions. Public understanding and attitudes, often influenced by cultural and social norms, impact the adoption of these technologies. In the case of the Women's Health Initiative (WHI) trials, the cultural context of the time and the portrayal of the results in the media influenced public perception and led to a significant decline in hormone therapy use. Public perceptions of the risks and benefits of these technologies can shape the adoption rates and preferences for different therapeutic options (Stefanick, 2005). The SCOT framework can be applied to the approval and opposition of hormonal health technologies, revealing how public

perceptions, shaped by cultural and social norms, can dynamically influence their adoption. The framework's concept of interpretative flexibility is evident as diverse public interpretations, influenced by societal norms, impact the adoption of these medical interventions. The Women's Health Initiative (WHI) trials illustrate SCOT's stabilization or closure of public perception, as the portrayal of trial results in the media, and the cultural context of the time, led to a significant decline in hormone therapy use. The recognition of media influence, emphasizing its role in shaping public perceptions and contributing to the stabilization of attitudes toward hormonal health technologies, mirrors SCOT's emphasis on external mediators. SCOT's principles become evident as the media played a crucial role in stabilizing public perception and contributing to a significant decline in hormone therapy use, showcasing the framework's relevance in understanding the multifaceted relationship between societal influences and technological adoption.

Moreover, the application of SCOT underscores the profound influence of cultural and social norms on technological development. Public understanding and attitudes, as highlighted, are molded by these norms, impacting the adoption of hormonal health technologies. SCOT is highly relevant in analyzing the socio-psychological determinants of technology acceptance, including perceived risk, benefit, trust, culpability, knowledge, individual differences, and attitude (Gupta et al., 2012). In conclusion, SCOT's recognition of the profound impact of cultural and social norms on public understanding and attitudes, particularly in the context of hormonal health technologies, highlights its significance in comprehensively analyzing the socio-psychological determinants of technology acceptance and shaping an understanding of the intricate relationship between societal factors and technological adoption.

The use of technologies for hormonal health monitoring, including advanced diagnostic tools and hormone-based therapies, has sparked ethical and policy debates. In the context of estrogen's clinical evolution, Social Construction of Technology (SCOT) underlines the intertwined relationship between scientific advancements and societal influences. (Pinch & Bijker, 1984; Santen & Simpson, 2019). The narrative surrounding hormonal health technologies is socially constructed, shaped by accessibility, affordability, and cultural attitudes toward health interventions. Gender norms and expectations further contribute to the public's reception of these technologies. Policymaking becomes pivotal to align these advancements with societal values, ensuring accessibility and addressing concerns about privacy and long-term effects. In conclusion, ongoing collaboration among the public, medical professionals, and policymakers is imperative as technology progresses in the realm of hormonal health, guiding ethical considerations and effective policy frameworks.

Conclusion

Estradiol's significance spans societal, scientific, and medical dimensions, revealing a connection between hormonal health technologies and the socio-political landscape. Sociocultural norms, gender identities, and public perceptions significantly influence the acceptance and resistance of these technologies, aligning with the social construction of scientific facts. SCOT emphasizes the reciprocal connection between technological development and societal influences, portraying the adoption of pivotal medical interventions like estradiol as a socially negotiated process. This underscores the need for nuanced ethical considerations and policy influences in shaping the adoption and regulation of these interventions. The predictive model and experimental component hold significance in streamlining research methodologies related to estradiol, offering efficient data predictions, and potentially reducing financial and

temporal burdens. Reflecting the estrous cycle stages, this model presents a promising alternative to labor-intensive vaginal cytology, especially beneficial in women's health research and future estradiol studies. It is crucial to recognize the relationship of sociocultural, ethical, and scientific influences shaping the landscape of hormonal health technologies, emphasizing the necessity for a comprehensive understanding that transcends the boundaries between science and society.

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