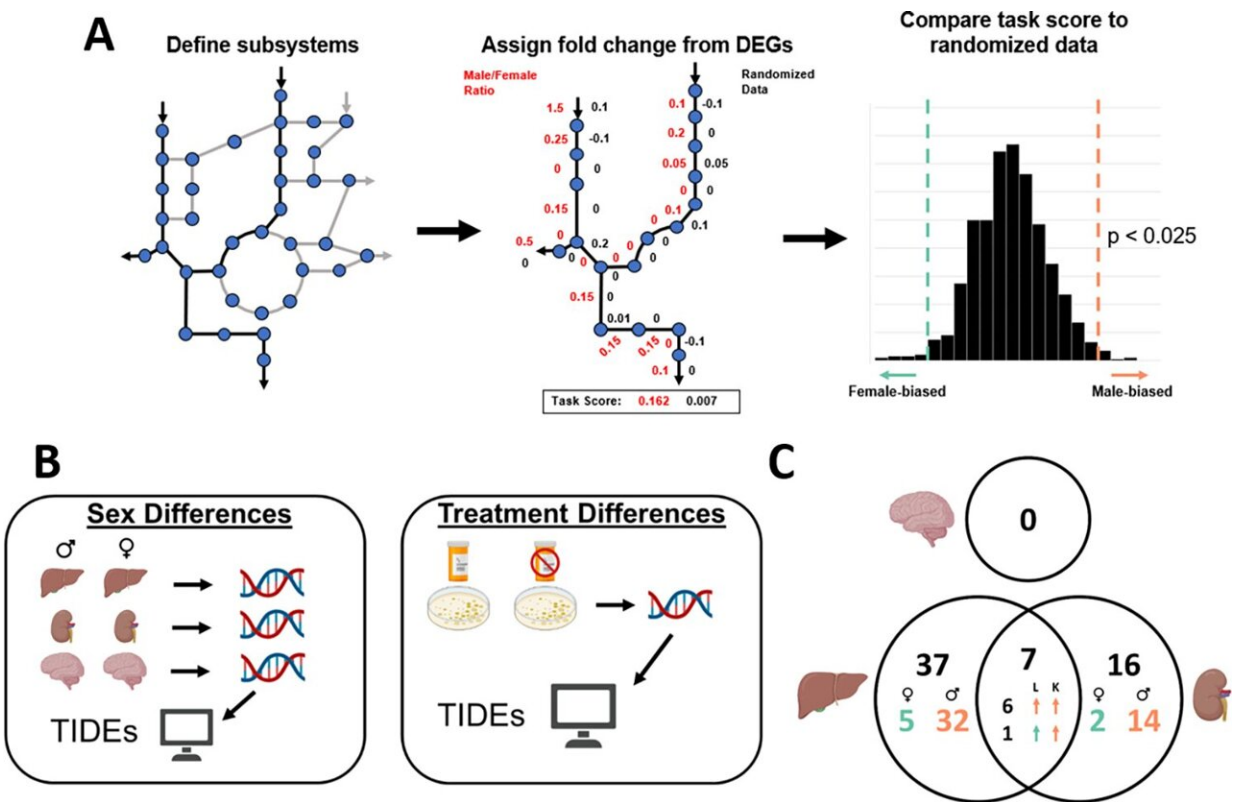


New tool reveals how drugs affect men, women differently, and could lead to safer medications

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(A) Tasks Inferred from Differential Expression (TIDES) is summarized. First, reactions are delineated as part of a metabolic subsystem. Expression data and GPRs are then used to assign log₂ fold changes as weights to each reaction. The TIDES score is then calculated as the average weight of the subsystem and compared to randomized fold changes from other genes in the data to determine significance. (B) This method is used to compare sex-specific untreated liver, kidney, and brain expression data as well as treated and untreated cultured

hepatocyte expression data. (C) 37 subsystems are sex-biased exclusively in the liver, 16 are sex-biased exclusively in the kidney, and 0 are sex-biased in the brain. 7 subsystems are altered by sex in both the liver and kidney, with 6 upregulated in males in both tissue types, and 1 upregulated in the female liver and male kidney. Created with BioRender.com. Credit: *PLOS Computational Biology* (2023). DOI: 10.1371/journal.pcbi.1010927

UVA Health researchers have developed a powerful new tool to understand how medications affect men and women differently, and that will help lead to safer, more effective drugs in the future.

Women are known to suffer a disproportionate number of liver problems from medications. At the same time, they are typically underrepresented in [drug testing](#). To address this, the UVA scientists have developed sophisticated computer simulations of male and female livers and used them to reveal [sex-specific differences](#) in how the tissues are affected by drugs.

The new model has already provided unprecedented insights into the [biological processes](#) that take place in the liver—the organ responsible for detoxifying the body—in both men and [women](#). But the model also represents a powerful new tool for [drug development](#), helping ensure that new medications will not cause harmful side effects.

"There are incredibly complex networks of genes and proteins that control how cells respond to drugs," said UVA researcher Jason Papin, Ph.D., one of the model's creators. "We knew that a [computer model](#) would be required to try to answer these important clinical questions, and we're hopeful these models will continue to provide insights that can improve health care."

Harmful effects from drugs

Papin, of UVA's Department of Biomedical Engineering, developed the model in collaboration with Connor Moore, a Ph.D. student, and Christopher Holstege, MD, a UVA emergency medicine physician and director of UVA Health's Blue Ridge Poison Center. "It is exceedingly important that both men and women receive the appropriate dose of recommended medications," Holstege noted. "Drug therapy is complex and toxicity can occur with subtle changes in dose for specific individuals."

Before developing their model, the researchers first looked at the federal Food and Drug Administration's Adverse Event Reporting System to evaluate the frequency of reported [liver problems](#) in men and women. The scientists found that women consistently reported liver-related adverse events more often than men.

The researchers then sought to explain why this might be the case. To do that, they developed computer models of the male and female livers that integrated vast amounts of data on gene activity and metabolic processes within cells. These cutting-edge liver simulations provided important insights into how drugs affect the tissue differently in men and women and allowed the researchers to understand why.

"We were surprised how many differences we found, especially in very diverse biochemical pathways," said Moore, a [biomedical engineering](#) student in Papin's lab. "We hope our results emphasize how important it is for future scientists to consider how both men and women are affected by their research."

The work has already identified a key series of cellular processes that explain sex differences in liver damage, and the scientists are calling for more investigation of it to better understand "hepatotoxicity"—liver

toxicity. Ultimately, they hope their model will prove widely useful in developing safer drugs.

"We're hopeful these approaches will help address many other questions where men and women have differences in drug responses or disease processes," Papin said. "Our ability to build predictive computer models of complex systems in biology, like those in this study, is truly opening all kinds of new avenues for tackling some of the most challenging biomedical problems."

The researchers have [published their findings in *PLOS Computational Biology*](#).

More information: Connor J. Moore et al, Metabolic modeling of sex-specific liver tissue suggests mechanism of differences in toxicological responses, *PLOS Computational Biology* (2023). [DOI: 10.1371/journal.pcbi.1010927](#)

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