**Case Study Report**

**Patent Title:**

**METHOD FOR PREDICTING ORGAN TOXCITY AND A SYSTEM THEREOF**

**Patent Number:** US 8,645,075 B2

**Filing Date:** Dec. 9, 2009

**Applicants:** Strand Life Sciences PVT Ltd.

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**Introduction**

This patent describes a computer-based method and system for predicting how drugs (or chemicals) might harm human organs—especially the liver—before those drugs are given to people. The system combines computer models ("in silico") with lab experiments ("in vitro") to simulate and predict organ toxicity in a detailed, mechanistic way.

**Why Is This Important?**

Drug development is risky and expensive. Many drugs fail late in the process because they turn out to be toxic to organs like the liver. Traditional methods—like animal testing or simple statistical models—often miss these problems or can't explain them. This patent aims to make toxicity prediction more reliable, accurate, and explainable by modeling the actual biology of the organ, not just looking for patterns in past data.

**How Does the System Work?**

**1. Building a Digital Model of the Organ**

* The inventors first gather detailed information about how drugs can injure organs, focusing on the underlying biochemical pathways and mechanisms (for example, how a drug might disrupt energy production or antioxidant defenses in the liver).
* They identify key molecules and enzymes involved in these processes and collect data about their normal levels and activity.
* Using this information, they construct a mathematical model—a set of equations that describe how these molecules and pathways interact to maintain a healthy, stable state (homeostasis) in the organ.

**2. Simulating Drug Effects**

* The model can be "perturbed"—meaning the inventors can simulate what happens if a drug interferes with a particular enzyme or pathway.
* These perturbations can mimic real-world drug effects, such as blocking energy production (leading to cell death), causing fat buildup (steatosis), or blocking bile flow (cholestasis)1.
* The model predicts how the concentrations of key molecules will change, and whether these changes cross thresholds associated with toxicity.

**3. Designing and Integrating Lab Tests**

* Based on the model, the inventors design laboratory assays to measure how a drug actually affects key enzymes or pathways in cells.
* Data from these assays are fed back into the model, refining predictions and allowing for more personalized or chemical-specific toxicity forecasts.

**What Makes This Approach Different?**

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| --- | --- | --- |
| **Feature** | **Traditional Models (e.g., QSAR)** | **This Patent's System** |
| Basis | Statistical patterns in past data | Mechanistic, biology-based modeling |
| Flexibility | Limited to known chemical space | Can simulate new drugs, new pathways |
| Explanation of Toxicity | Often a "black box" | Provides mechanistic explanations |
| Applicability to Different Organs | Usually specific | Adaptable to many organs |
| Use of Experimental Data | Sometimes, but limited | Actively integrates new lab data |

**Examples from the Patent**

* Simulating Mitochondrial Damage: The model can predict how blocking mitochondrial ATP production (the cell's energy source) leads to cell death, as seen with some painkillers.
* Modeling Cholestasis: By simulating the effect of blocking bile salt transport, the model predicts the buildup of bile acids in blood and urine, matching real-world observations.

**Reference**

Subramanian, K., Raghavan, S., Bhat, A. R., Das, S., Dikshit, J. B., Kumar, R., Krishnakumar, N. M., Rajeshwara, N., Radhakrishnan, R., & Raghunathan, S. (2014). *Method for predicting organ toxicity and a system thereof* (U.S. Patent No. 8,645,075 B2). U.S. Patent and Trademark Office.

**Case Study Paper:**

**Title :**

**Understanding DILIPredictor: A New Approach to Predicting Drug-Induced Liver Injury**

**Authors:** Srijit Seal, Dominic Williams, Layla Hosseini-Gerami, Manas Mahale, Anne E. Carpenter, Ola Spjuth,\* and Andreas Bender\*

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**Introduction**

Drug-induced liver injury (DILI) represents one of the most significant challenges in drug development, often becoming apparent only in late-stage clinical trials or after a drug reaches the market. Recently, researchers developed a new model called DILIPredictor that aims to better identify compounds that might cause liver damage. This report explains this research and its potential impact on drug safety assessment.

**The Problem: Why Liver Toxicity Matters**

The liver plays a crucial role in metabolizing drugs in our bodies, which unfortunately makes it vulnerable to drug-related damage. DILI accounts for over 50% of acute liver failure cases and is a leading reason why drugs fail in late-stage clinical trials or get withdrawn after market approval1. This creates a major challenge for pharmaceutical companies:

* Detecting liver toxicity early could save billions in development costs
* Traditional testing methods often fail to predict human liver reactions accurately

**The Research Approach: Combining Multiple Data Sources**

The researchers hypothesized that combining different types of data would create a more accurate prediction model. Their approach, called DILIPredictor, integrates:

**Chemical structure information:**

* Molecular fingerprints that represent chemical structures
* Physicochemical properties like molecular weight and solubility

**Biological data:**

* In vitro data (cell-based tests) like mitochondrial toxicity
* In vivo data (animal studies) from preclinical testing

**Key Findings: Better Detection of Dangerous Compounds**

When tested on 223 compounds not seen during training:

* DILIPredictor achieved an AUC-ROC score of 0.63 and a positive likelihood ratio of 1.40
* The model was particularly good at identifying the most toxic compounds with fewer false positives
* For the top 25 toxic compounds, DILIPredictor achieved a positive likelihood ratio of 2.68 compared to 1.65 for models using only structural features.

This improved detection is crucial for pharmaceutical companies needing to identify problematic compounds early in development.

**Real-World Examples**

The model correctly identified several challenging cases:

1. **Sitaxentan**: This drug was withdrawn from the market due to liver toxicity. DILIPredictor correctly flagged it as toxic, specifically highlighting the sulfonamide chemical group that likely contributes to its toxicity.
2. **2-Butoxyethanol**: This compound causes liver toxicity in mice but not humans. DILIPredictor correctly predicted it as safe for humans despite its toxicity in animal models, demonstrating its ability to differentiate between species sensitivity.

**Reference**

1. Seal, S., Williams, D., Hosseini-Gerami, L., Mahale, M., Carpenter, A. E., Spjuth, O., & Bender, A. (2024). Improved Detection of Drug-Induced Liver Injury by Integrating Predicted In Vivo and In Vitro Data. Chemical Research in Toxicology, 37(8), 1290-1305. [ttps://pubs.acs.org/doi/10.1021/acs.chemrestox.4c00015[](https://pubs.acs.org/doi/10.1021/acs.chemrestox.4c00015)]