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Stability and bifurcation analysis in mathematical models for oscillating pregnane X receptor levels

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The pregnane X receptor (PXR) is a nuclear receptor that plays a key role in regulating metabolic enzymes and transporters. In various species [1] and under different regulatory mechanisms [2], PXR may exhibit oscillatory behavior in its mRNA concentration. These oscillations can lead to variations in corresponding PXR-controlled drug-handling enzyme expression levels, thereby influencing drug metabolic pathways.

Here, we develop mathematical models to explore two possible drivers of PXR oscillations: circadian rhythm and negative feedback loop. The circadian rhythm model demonstrates how rhythmic inputs from the circadian clock can affect PXR activity. The negative feedback loop model assumes that activated PXR downregulates its gene expression, possibly generating oscillations in PXR mRNA concentrations. A stability analysis in the negative feedback loop model aims to identify the parameter sets that lead to stable or unstable solutions. A bifurcation analysis determines a parameter region where a small change in kinetic or regulatory parameters shifts the system from a stable steady state to limit cycle oscillations.

For instance, the Hill coefficient associated with the feedback loop term serves as the bifurcation parameter, following a Hopf bifurcation. The parameters derived from the mathematical model, related to drug pharmacokinetics,

PXR dynamics, and enzyme kinetics, provide insights into the conditions and periodicity of oscillations in related proteins. These findings enhance our understanding of PXR dynamics and their impact on metabolic regulation and drug response.

Clinically, these information may help in decision-making for determining optimal therapeutic dosages and designing effective multi-drug treatment strategies, especially when the drugs are metabolized by the same cytochrome P450 enzyme.

Keywords: pregnane X receptor, CYP450 enzymes, circadian clock, auto-feedback loops, stability analysis, bifurcation analysis

References

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