

□ 1: [Theor Biol Med Model](#). 2008 Apr 28;5:8.

### A mathematical model of glutathione metabolism.

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**BACKGROUND:** Glutathione (GSH) plays an important role in anti-oxidant defense and detoxification reactions. It is primarily synthesized in the liver by the transsulfuration pathway and exported to provide precursors for in situ GSH synthesis by other tissues. **Deficits in glutathione have been implicated in aging and a host of diseases including Alzheimer's disease, Parkinson's disease, cardiovascular disease, cancer, Down syndrome and autism.**

**APPROACH:** We explore the properties of glutathione metabolism in the liver by experimenting with a mathematical model of one-carbon metabolism, the transsulfuration pathway, and glutathione synthesis, transport, and breakdown. The model is based on known properties of the enzymes and the regulation of those enzymes by oxidative stress. We explore the half-life of glutathione, the regulation of glutathione synthesis, and its sensitivity to fluctuations in amino acid input. We use the model to simulate the metabolic profiles previously observed in Down syndrome and autism and compare the model results to clinical data. **CONCLUSION:** We show that the glutathione pools in hepatic cells and in the blood are quite insensitive to fluctuations in amino acid input and offer an explanation based on model predictions. In contrast, we show that hepatic glutathione pools are highly sensitive to the level of oxidative stress. **The model shows that overexpression of genes on chromosome 21 and an increase in oxidative stress can explain the metabolic profile of Down syndrome.** The model also correctly simulates the metabolic profile of autism when oxidative stress is substantially increased and the adenosine concentration is raised. Finally, we discuss how individual variation arises and its consequences for one-carbon and glutathione metabolism.

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