Fig. 8. The saturation parameter θ_x^{μ} measures the normalized degree of saturation of the reaction at the steady state S^0. Shown is a Michaelis–Menten rate $\nu(S, K_M)$ (blue solid line), along with θ_x^{μ} (red dashed line) as a function of the steady state S^0/K_M.

Fig. 9. The Hill equation $\nu_{\mathrm{Hill}}(S)$ and the corresponding saturation parameter $\theta_x^{\mathrm{Hill}} \in [0, n]$ for a Hill coefficient $n = 4$ (both normalized to the unit interval). The saturation parameter θ_x^{Hill} measures increasing saturation of the reaction rate.

Fig. 10. The bifurcation diagram of the system at the (assumed) observed operating point. The two-dimensional pathway gives rise to a Hopf bifurcation and thus facilitates the emergence of sustained oscillations. (*Left*) The bifurcation diagram of the system at the operating point as a function of all three free saturation parameters. The blue surface denotes the Hopf bifurcation, above which the steady state (G^0, T^0) loses its stability. With increasing saturation (θ_{G}^2 and $\theta_{\mathrm{T}}^3 \to 0$) the (presumed) oscillatory region increases in size. The red surface denotes the emergence of a pair of complex conjugate eigenvalues; in between the red and blue surfaces the system exhibits an oscillatory return to the asymptotically stable steady state. (*Right*) A cut through the diagram at $\theta_{\mathrm{G}}^2 = 1$.

Fig. 11. The choice of the operating point. (*Left*) Often, in particular for oscillatory behavior, it can be assumed that the actual unstable state of the system is reasonably close to the average values. The deviation is exemplified here using the explicit model of the glycolytic pathway. The numerical simulation is shown as the solid blue line (parameters are as in Fig. 3*d*). (*Right*) Because we cannot assume precise knowledge of the actual unstable state, the analysis is repeated, including small (Gaussian) deviations of the observed average values (≈20%, shown as black dots).

Fig. 12. The eigenvalue with the largest real part as a function of the inhibitory strength ξ. All parameters are the same as in Fig. 3, only including a 20% variation in the (unstable) steady state (chosen from a Gaussian distribution centered at the average observed values). For each

inhibitory strength ξ, 10^4 instances of the Jacobian were evaluated. Shown is the average largest real part $\lambda_R^{\max}$ (solid blue line), along with the standard deviation (dashed red lines).

Fig. 13. Selecting for instances of the Jacobian that result in a stable operating point. (*Left*) The distribution of the largest real part within the spectrum of eigenvalues, corresponding to Fig. 4. All saturation parameters θ_x^μ are sampled randomly from a uniform distribution. (*Right Upper*) The initial distribution of the saturation parameter θ_{ATP}^8. (*Right Lower*) The distribution of the saturation parameter θ_{ATP}^8 when only instances of the Jacobians with $\lambda_R^{\max} < 0$ are selected from the initial ensemble.

Fig. 14. The distribution of saturation parameters when only instances of the Jacobian with $\lambda_R^{\max} < 0$ are selected from the initial ensemble. In each case, the parameter was initially selected from a uniform distribution.

Fig. 15. Convergence and dependence on ensemble size of the relative fraction of stable models as a function of the number of realizations of the Jacobian. All saturation parameters are sampled from a uniform distribution $\theta_x^\mu \in [0, 1]$.

Fig. 16. Distribution of the largest real part within the spectrum of eigenvalues for 5×10^5 random realizations of the photosynthetic Calvin cycle (solid line). The observed operating point is stable for the vast majority (≈94.3%) of possible kinetic parameters. When assuming a strong saturation of the triosephosphate isomerase with respect to GAP and a strong saturation of the G3P dehydrogenase on BPGA, the system becomes prone to instability (dashed line, $\theta_{\mathrm{GAP}}^{TPI} = \theta_{\mathrm{BPGA}}^{\mathrm{G3Pdh}} = 0.01$, ≈30% unstable models). Both values are known to be actually only weakly saturated (1), thus avoiding the instability.

1. Petterson, G. & Ryde-Petterson, U. (1988) Eur. J. Biochem. **175,** 661–672.

Fig. 17. The distribution of saturation parameters when only instances of the Jacobian with $\lambda_R^{\max} > 0$ are selected from the initial ensemble. Both parameters are sampled from a uniform distribution in the initial ensemble. To verify that both parameters indeed have a major impact on the stability of the system, Fig. 16 compares the distribution of eigenvalues when both parameters are restricted to high saturation to the initial (unrestricted) distribution of eigenvalues.