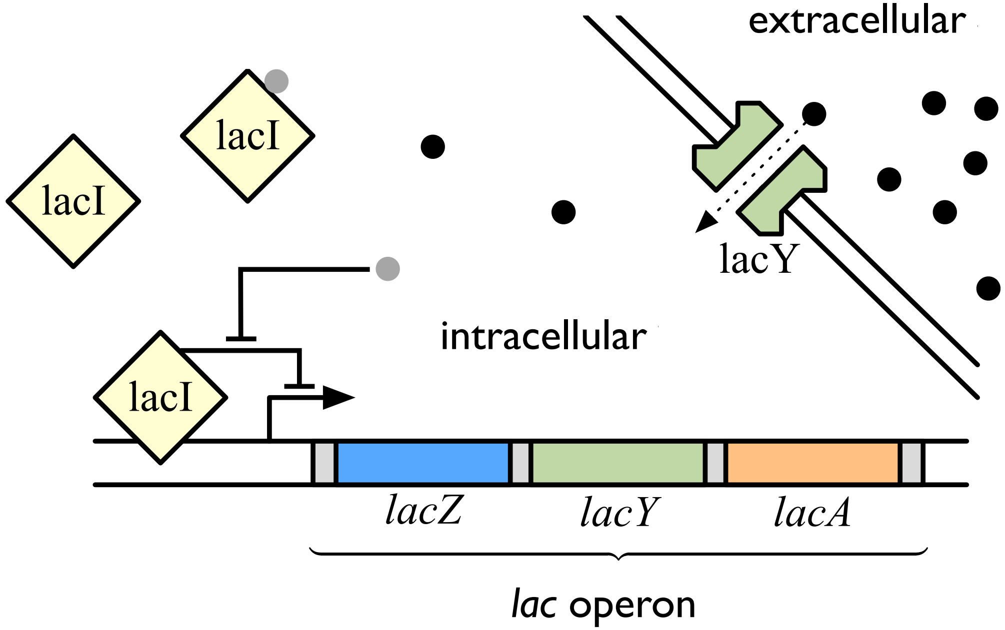
# Bistability in genetic networks generates hysteresis and bimodal behaviour

# Bistable behaviour in a genetic network relies on positive feedback and exhibits hysteresis

**Multistability in the lactose utilization network of *Escherichia coli***

Ertugrul M. Ozbudak[1]*, Mukund Thattai[1]*, Han N. Lim[1], Boris I. Shraiman[2] & Alexander van Oudenaarden[1]

Positive feedback is through the permease LacY, which acts to increase its own expression.



# Expression from the network exhibits hysteresis

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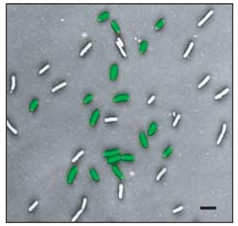
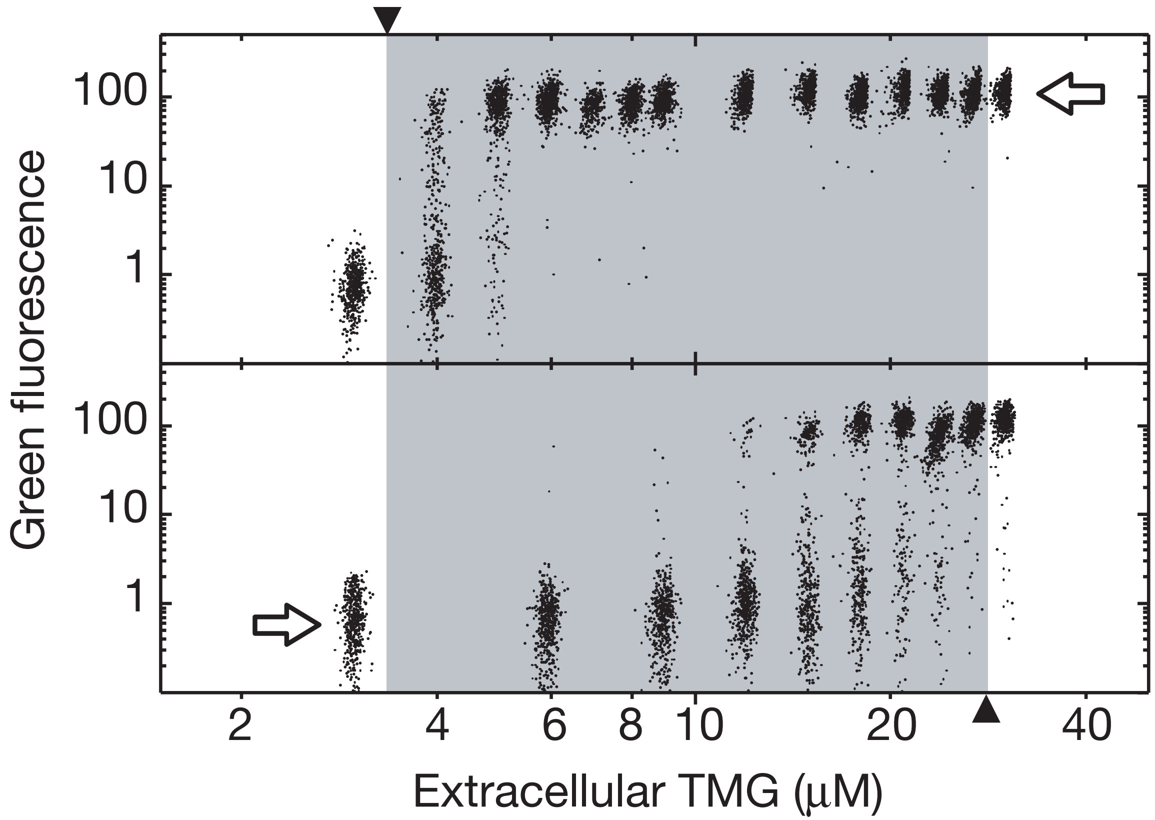
GFP synthesized from a copy of a promoter in the network is used to measure output.



Hysteresis: two different concentrations of inducer (TMG) cause switching of expression




Bimodal: the distribution of fluorescence has two peaks

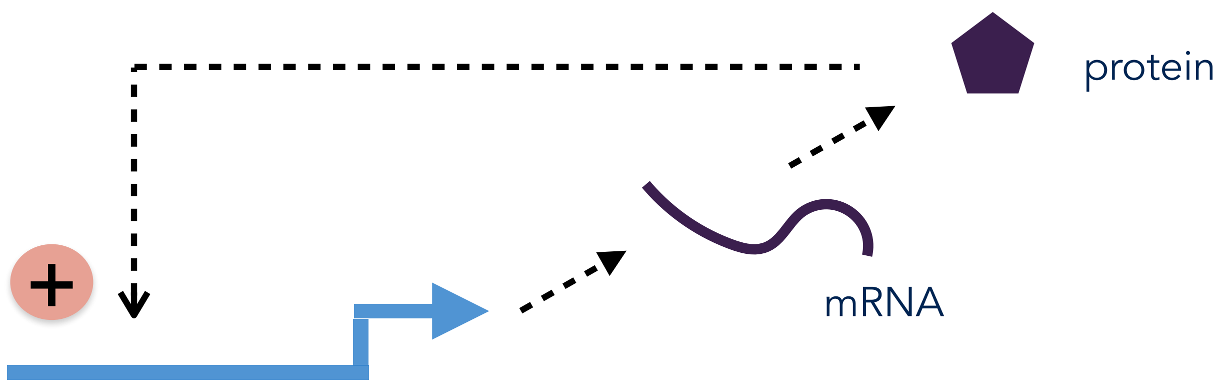
# Bistability may be generated by a transcription factor directly activating its own transcription

positive
feedback

mRNA $$\frac{dM}{dt} = u_b + \frac{uP^n}{K^n + P^n} - d_M M$$

protein $$\frac{dP}{dt} = M - d_P P$$

High levels of protein activate transcription creating still higher levels of protein.

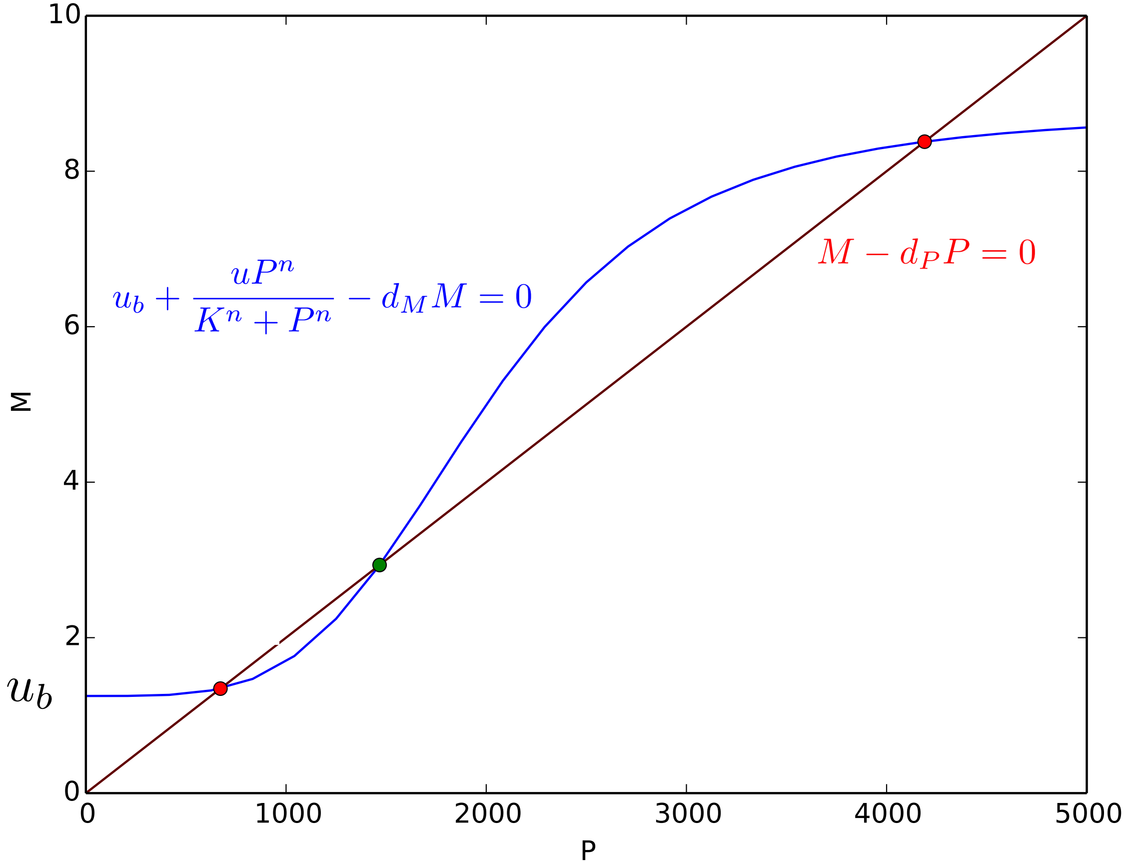


# The steady-states are where the nullclines intersect

The nullclines are the lines along which the time-derivative is zero.

$$\frac{dM}{dt} = u_b + \frac{uP^n}{K^n + P^n} - d_M M$$

$$\frac{dP}{dt} = M - d_P P$$



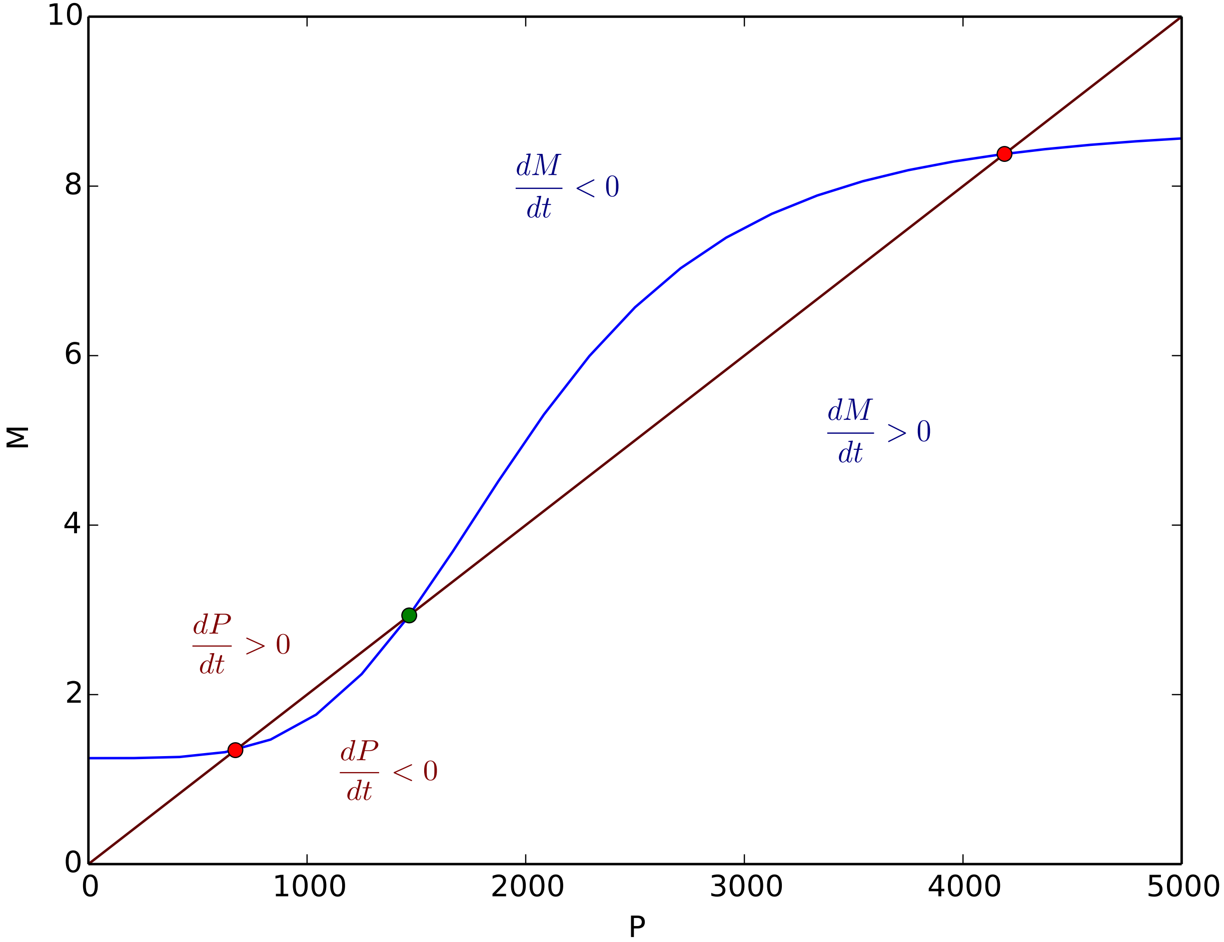

At the intersections of the nullclines, both *M* and *P* are at steady state because both *dM/dt* and *dP/dt* are zero.

On the blue nullcline, *dM/dt* is zero;
On the red nullcline, *dP/dt* is zero.

# We find the stability of the steady states by determining the local dynamics

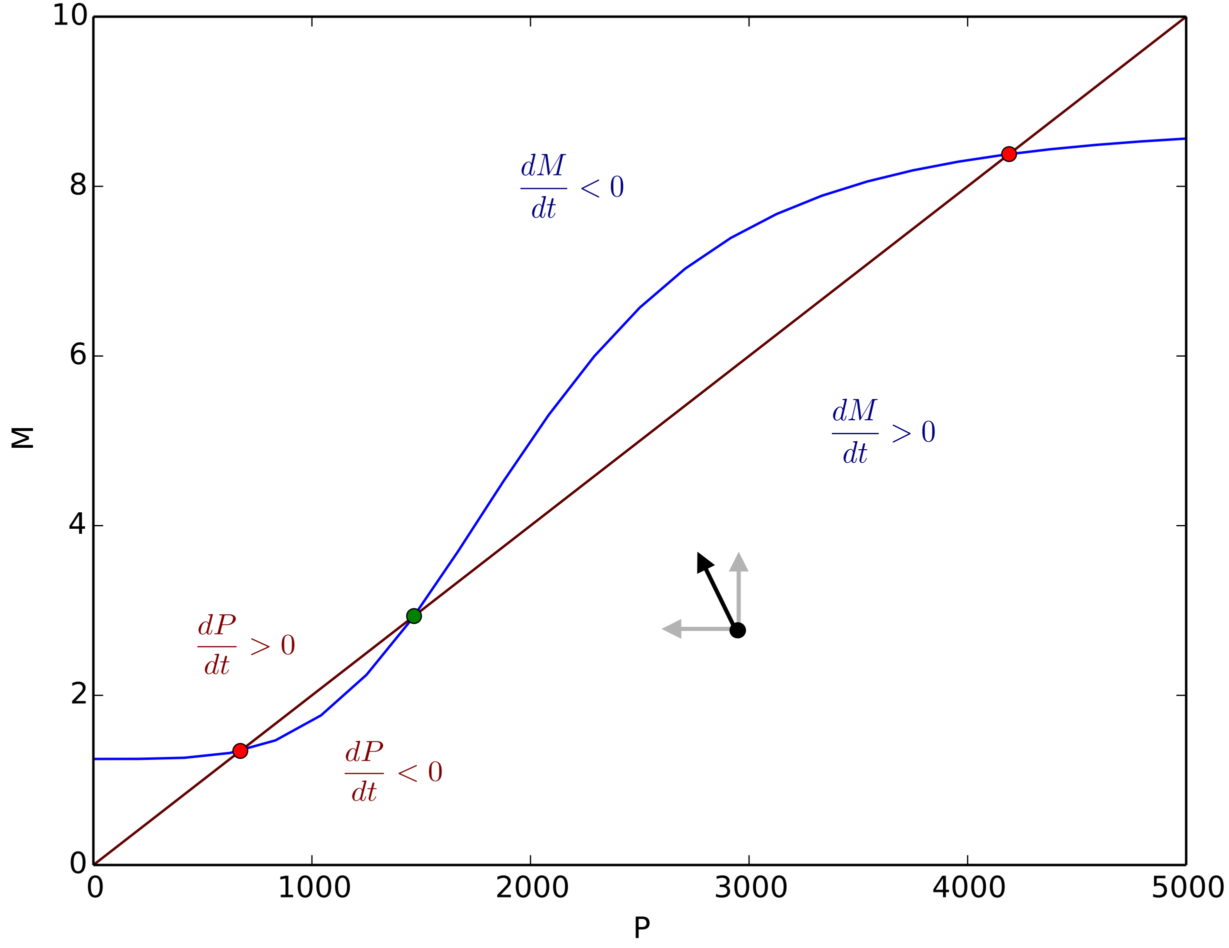
$$\frac{dM}{dt} = u_b + \frac{uP^n}{K^n+P^n} - d_M M$$

$$\frac{dP}{dt} = M - d_P P$$




On the blue nullcline,
*dM/dt* is zero;
On the red nullcline,
*dP/dt* is zero.

# We find the stability of the steady states by determining the local dynamics




On the blue nullcline, *dM/dt* is zero;
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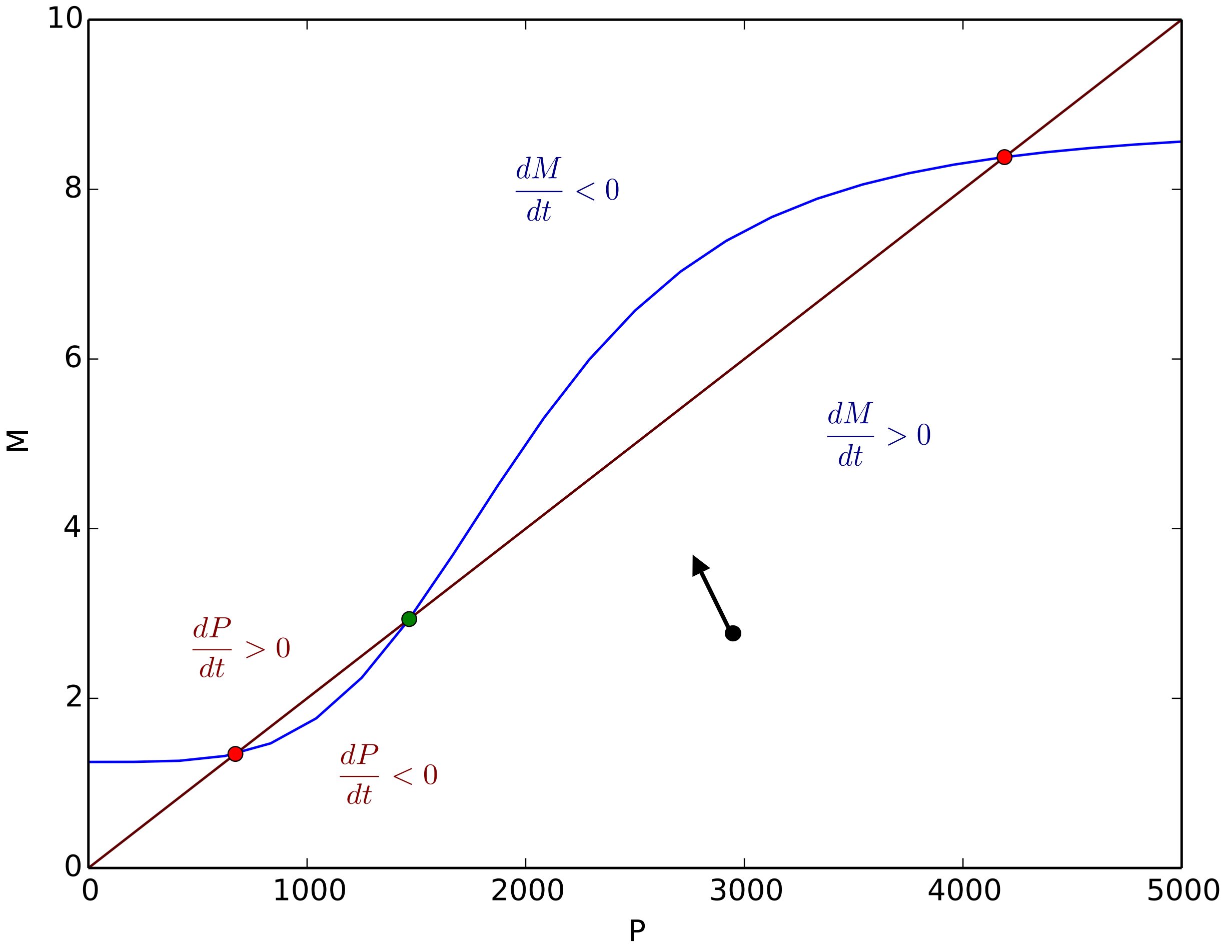


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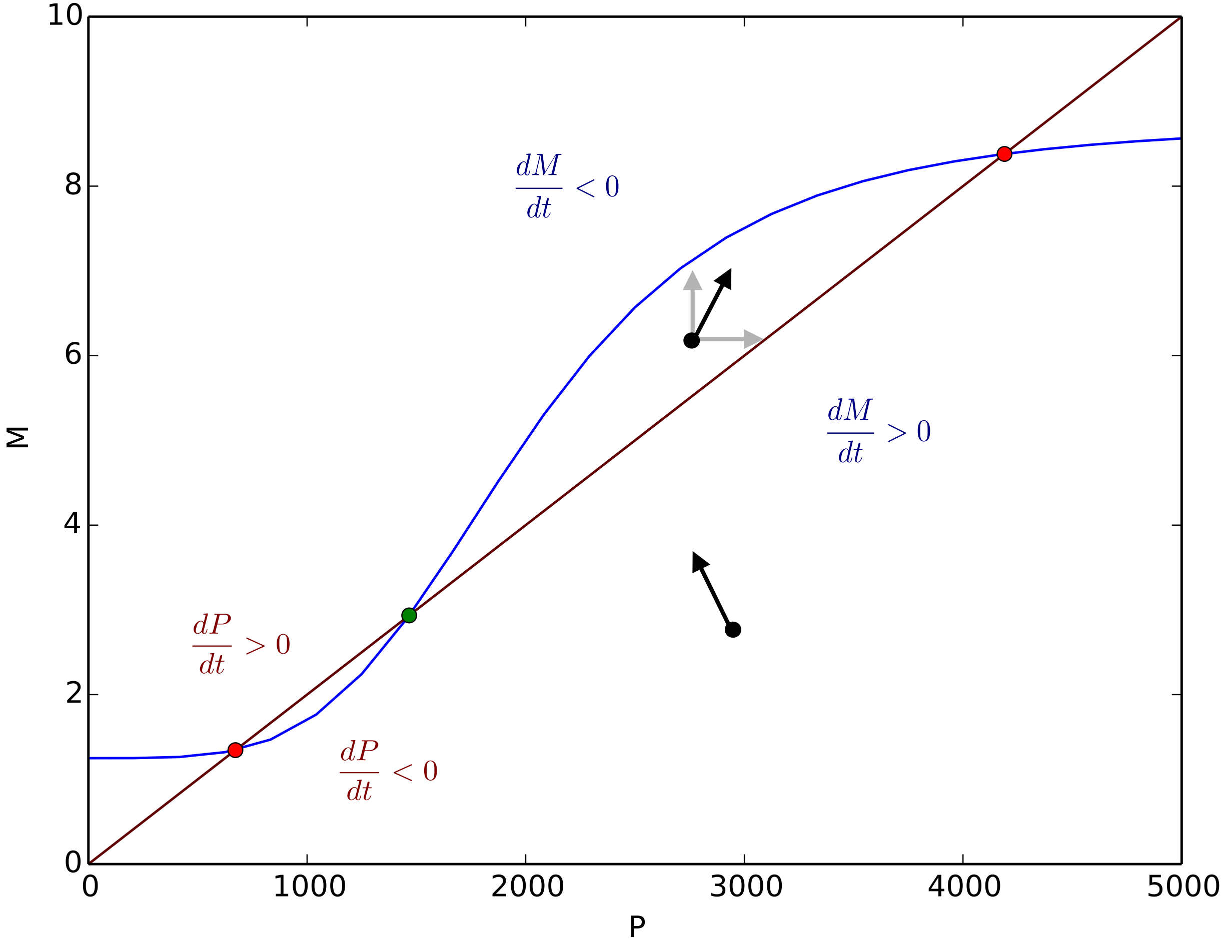


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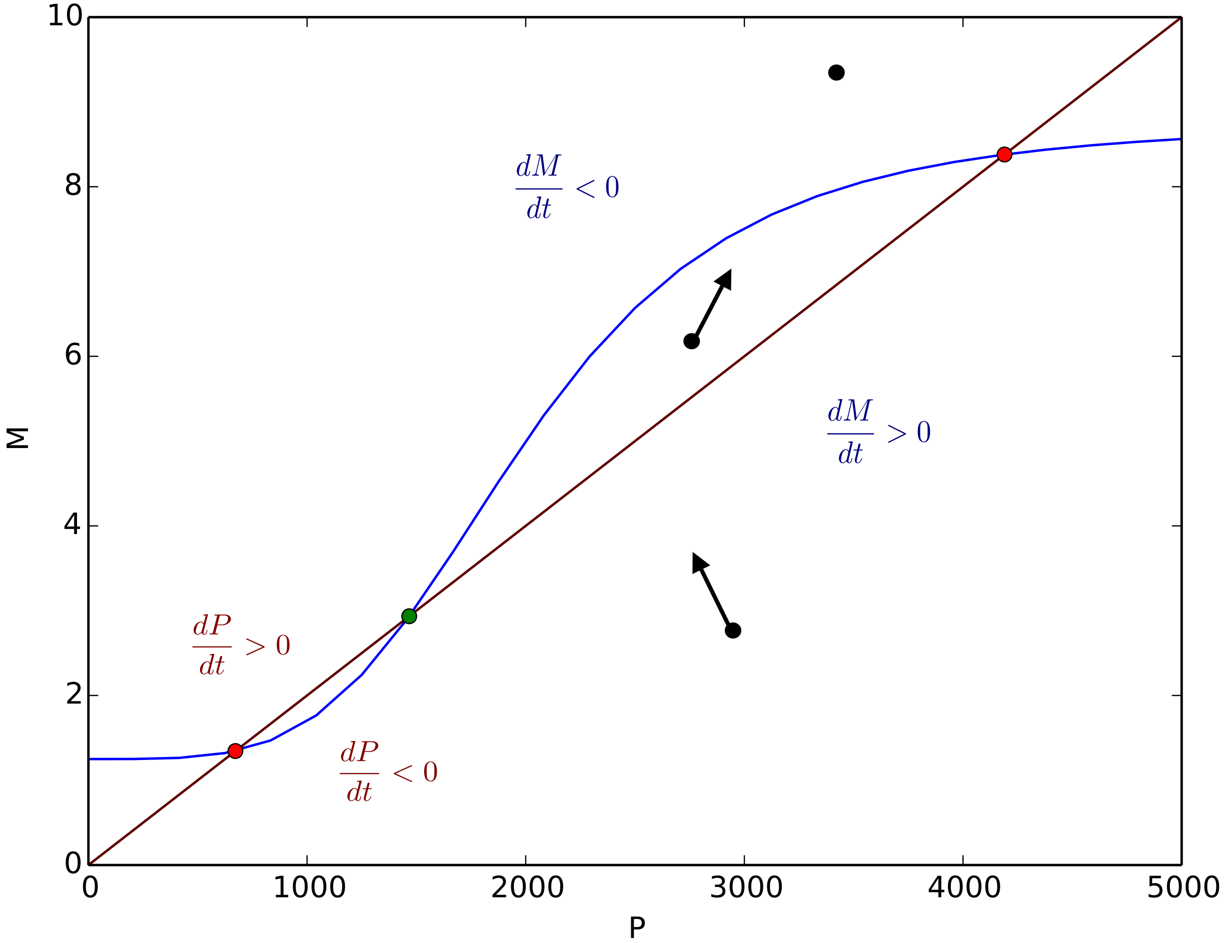


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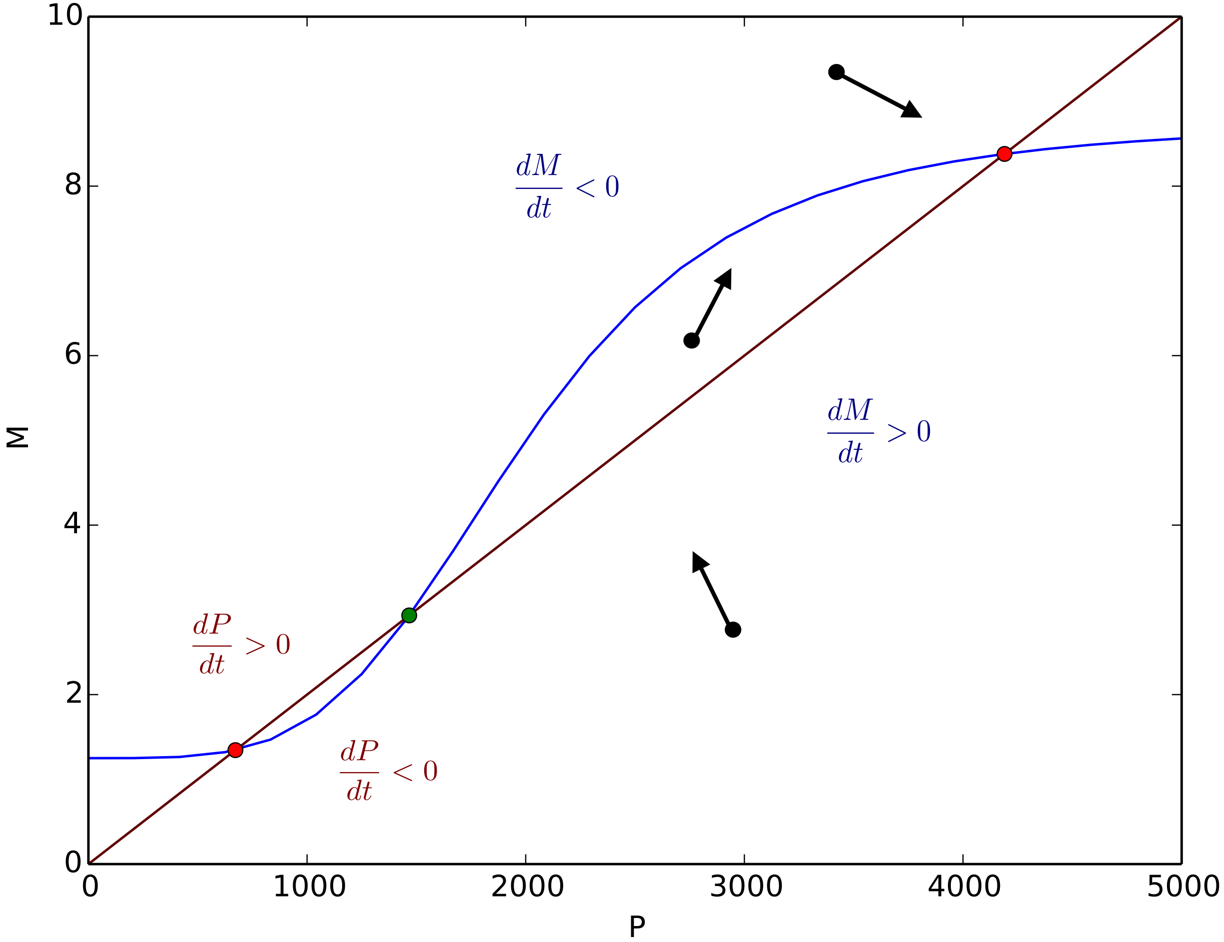
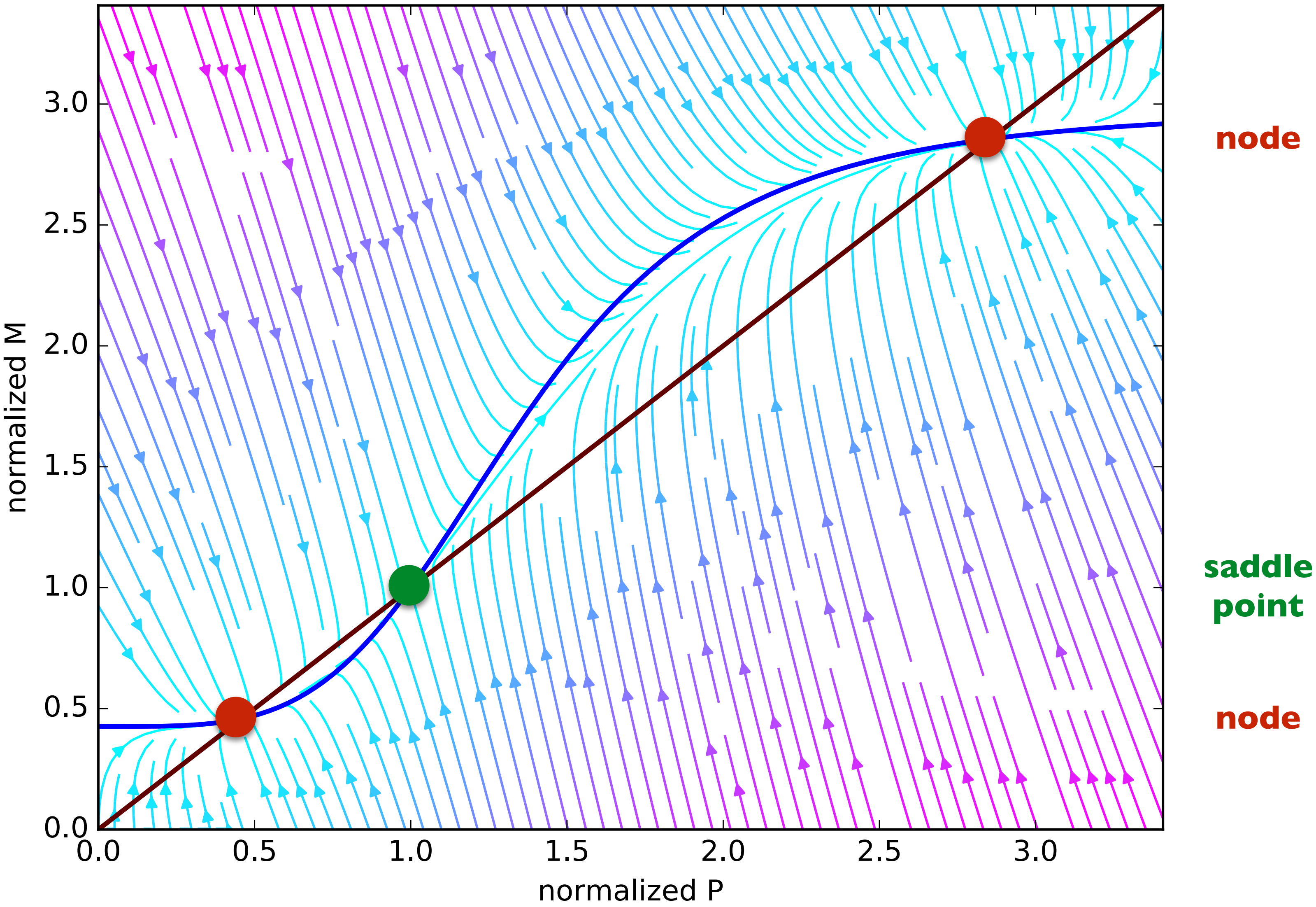
# We find the stability of the steady states by determining the local dynamics

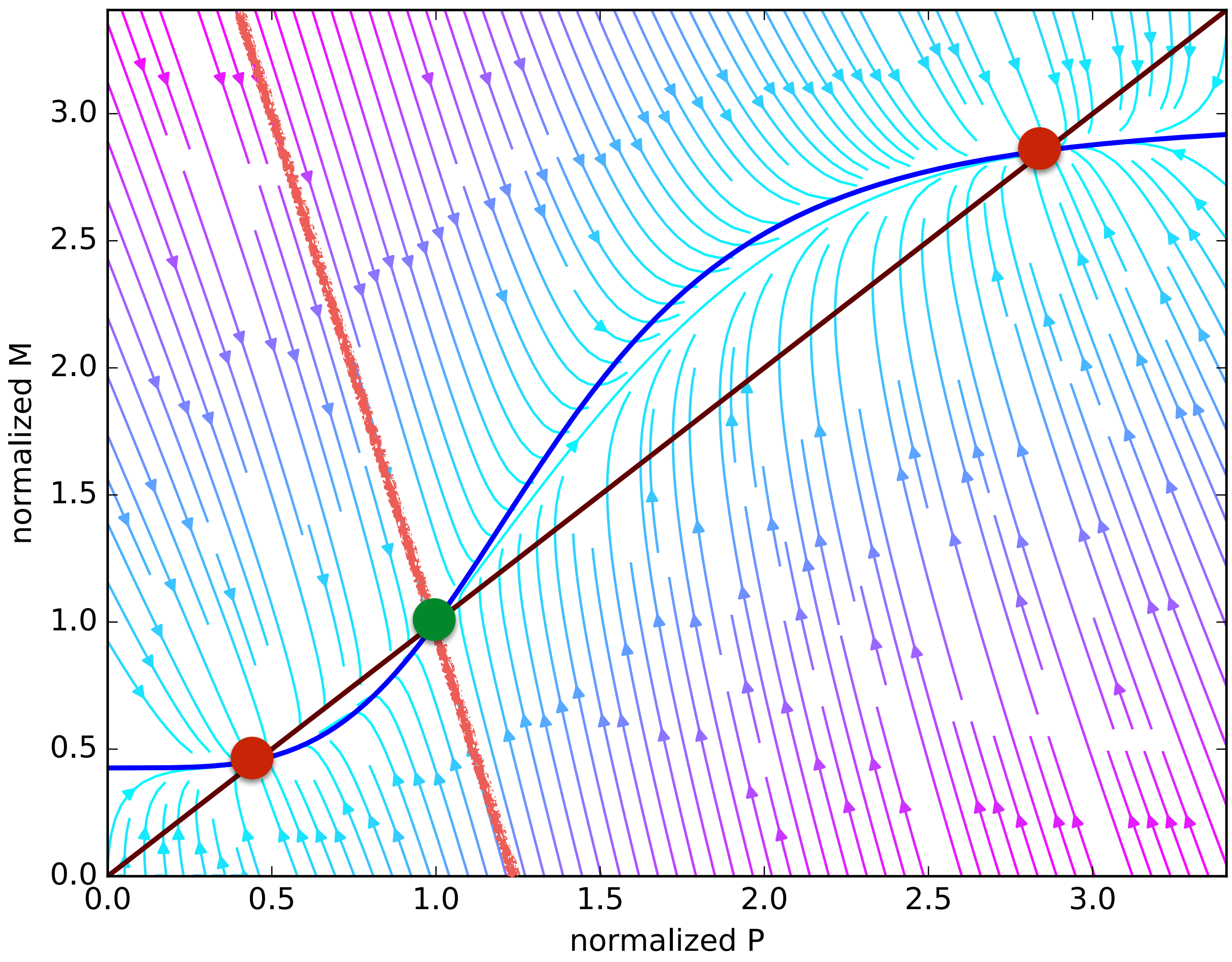



On the blue nullcline, *dM/dt* is zero;
On the red nullcline, *dP/dt* is zero.

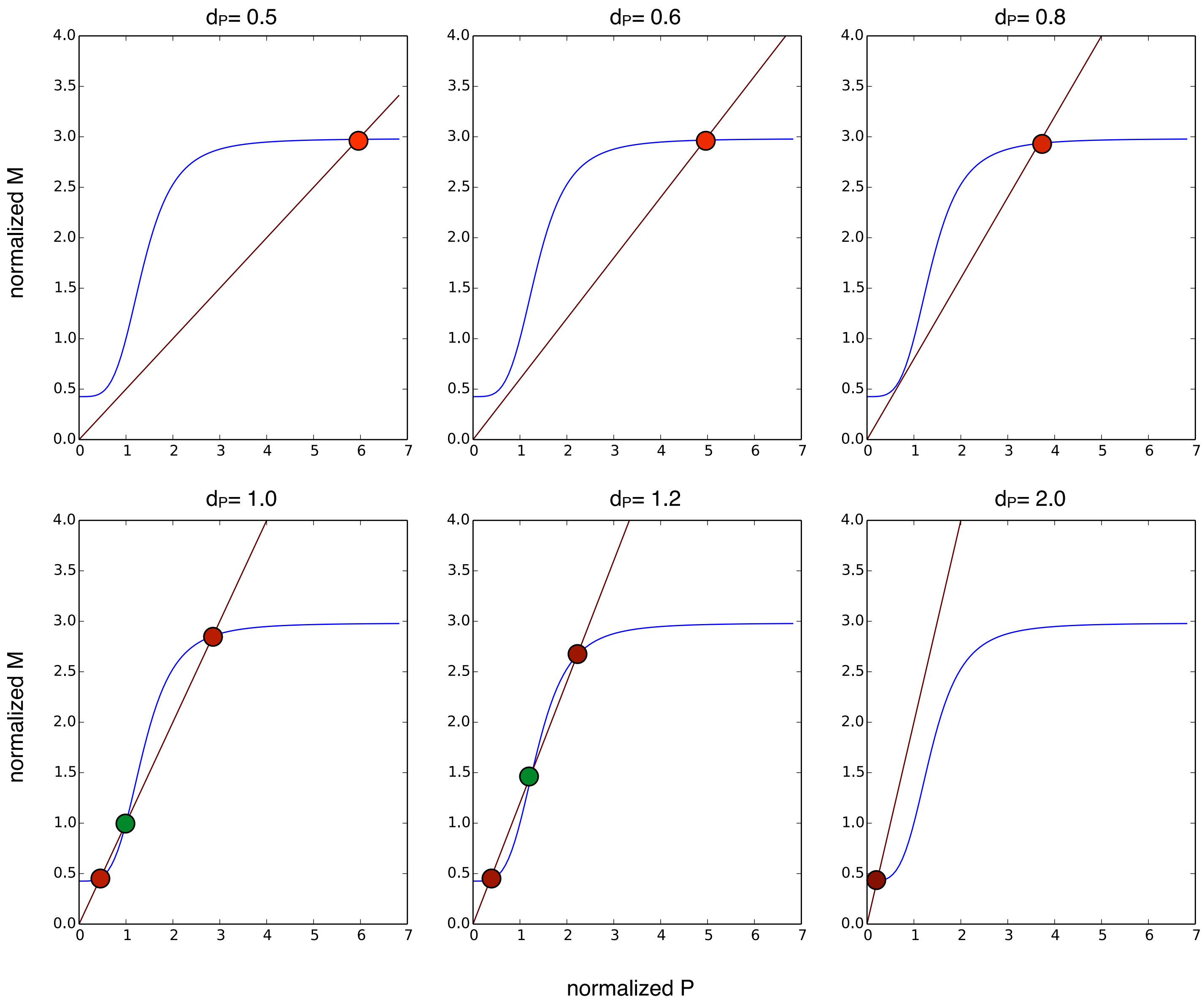
By systematically determining the local dynamics, we find two stable steady states and one unstable one



# The separatrix is the boundary between the two basins of attraction

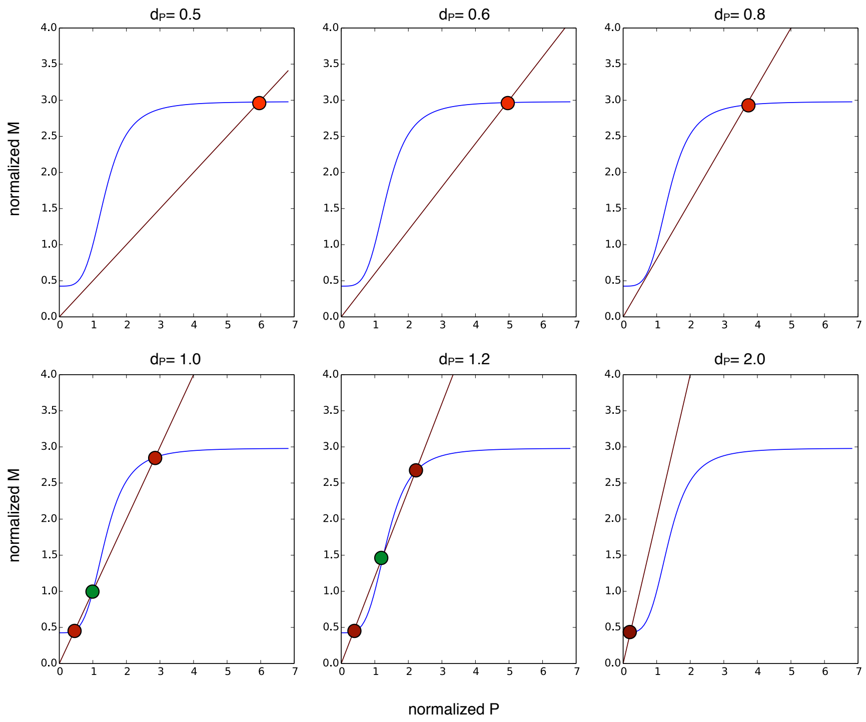


# The system can undergo a bifurcation from one to three steady states and vice versa



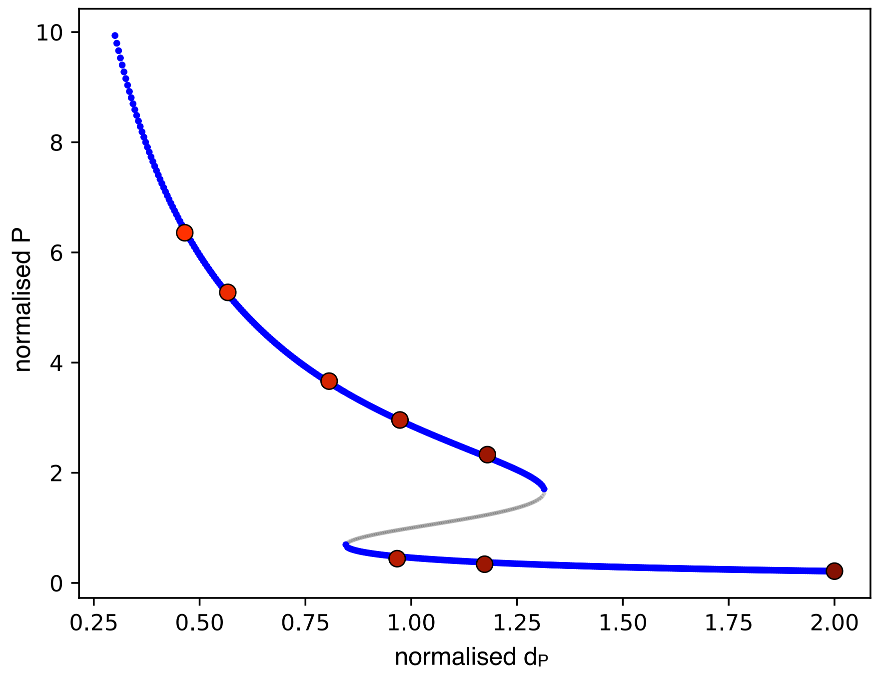

The protein degradation rate $d_P$ is the bifurcation parameter

# There are two saddle-node bifurcations

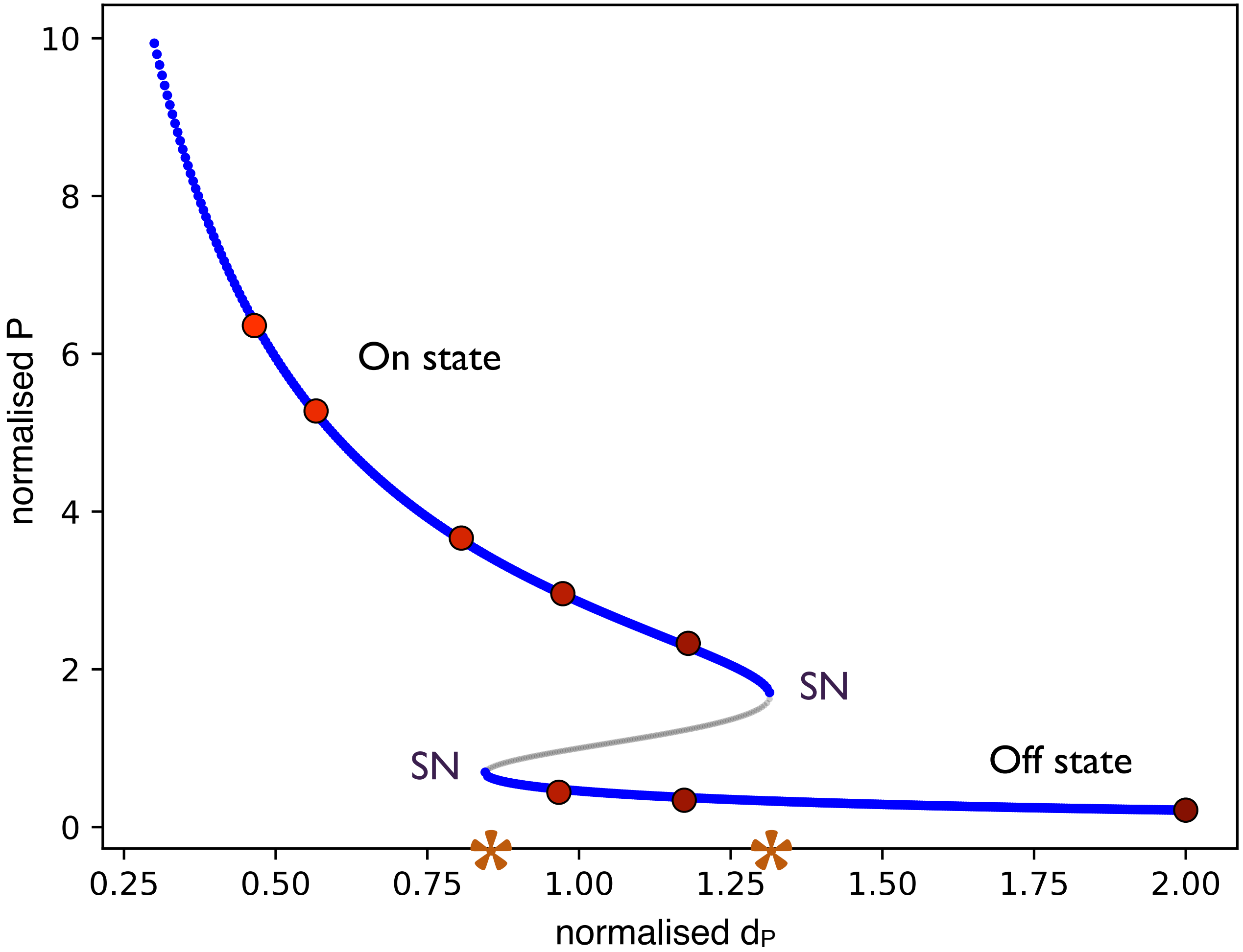



The protein degradation rate $d_P$ is the bifurcation parameter





# There is hysteresis, but the system is able to move from Off to On and from On to Off




The value of $d_P$ at which the system flips state (*) depends on whether $d_P$ is increasing or decreasing.

SN: saddle-node bifurcation