Transcriptional Regulation

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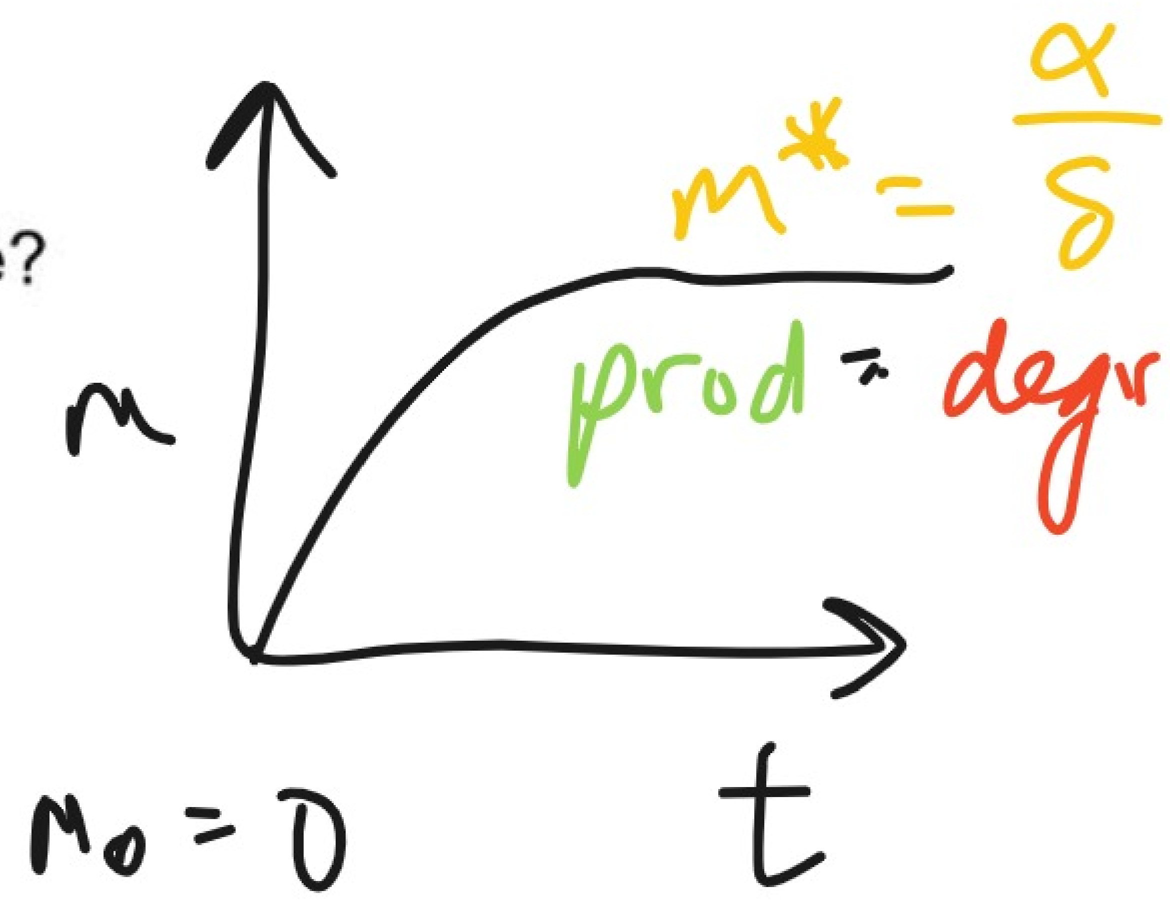
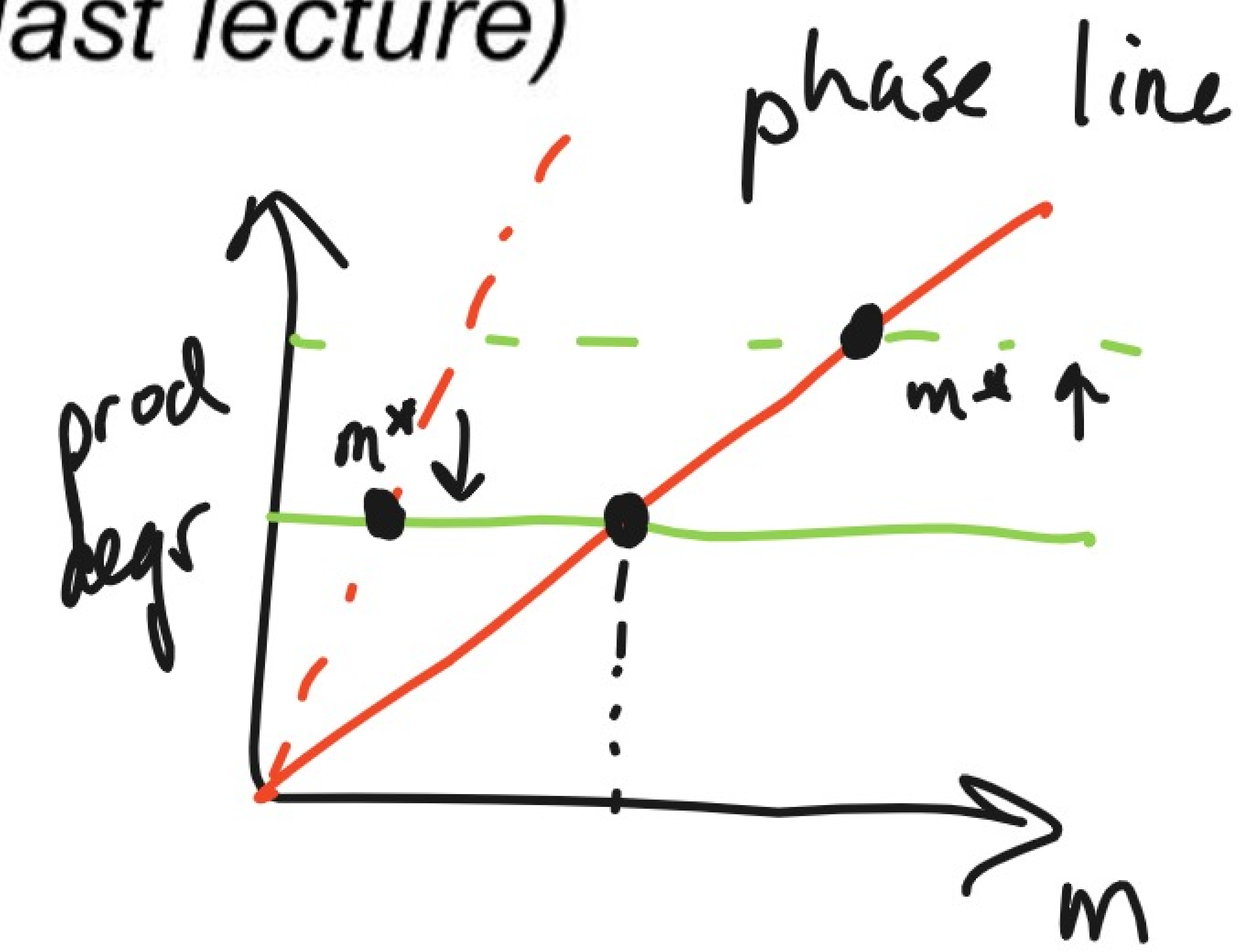
Analysis of the system for mRNA dynamics *(from last lecture)*

- How does steady state change?
- How does time to half steady state change?





Can visualize with **phase line**

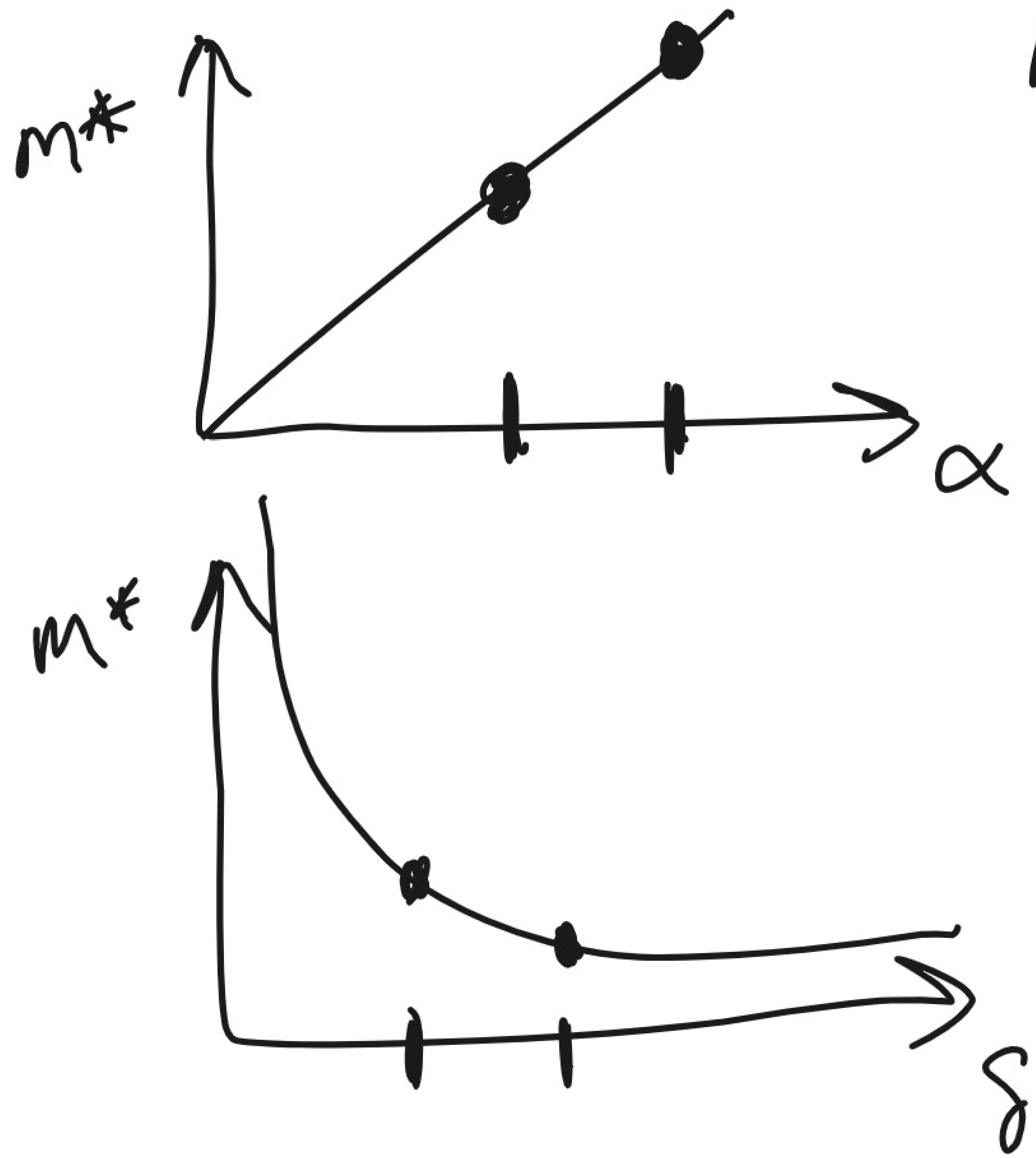
- Phase line is 1-D system
- x-axis is mRNA concentration
- y-axis is production/degradation
- Find intersection of two curves
- production = degradation

$$\frac{dm}{dt} = \alpha - \delta m$$

constant

Bifurcation of the system for mRNA dynamics *(from last lecture)*

- Graph of changes in steady state
  - Vary parameters (α, δ)
  - x-axis is parameter
  - y-axis is steady state value



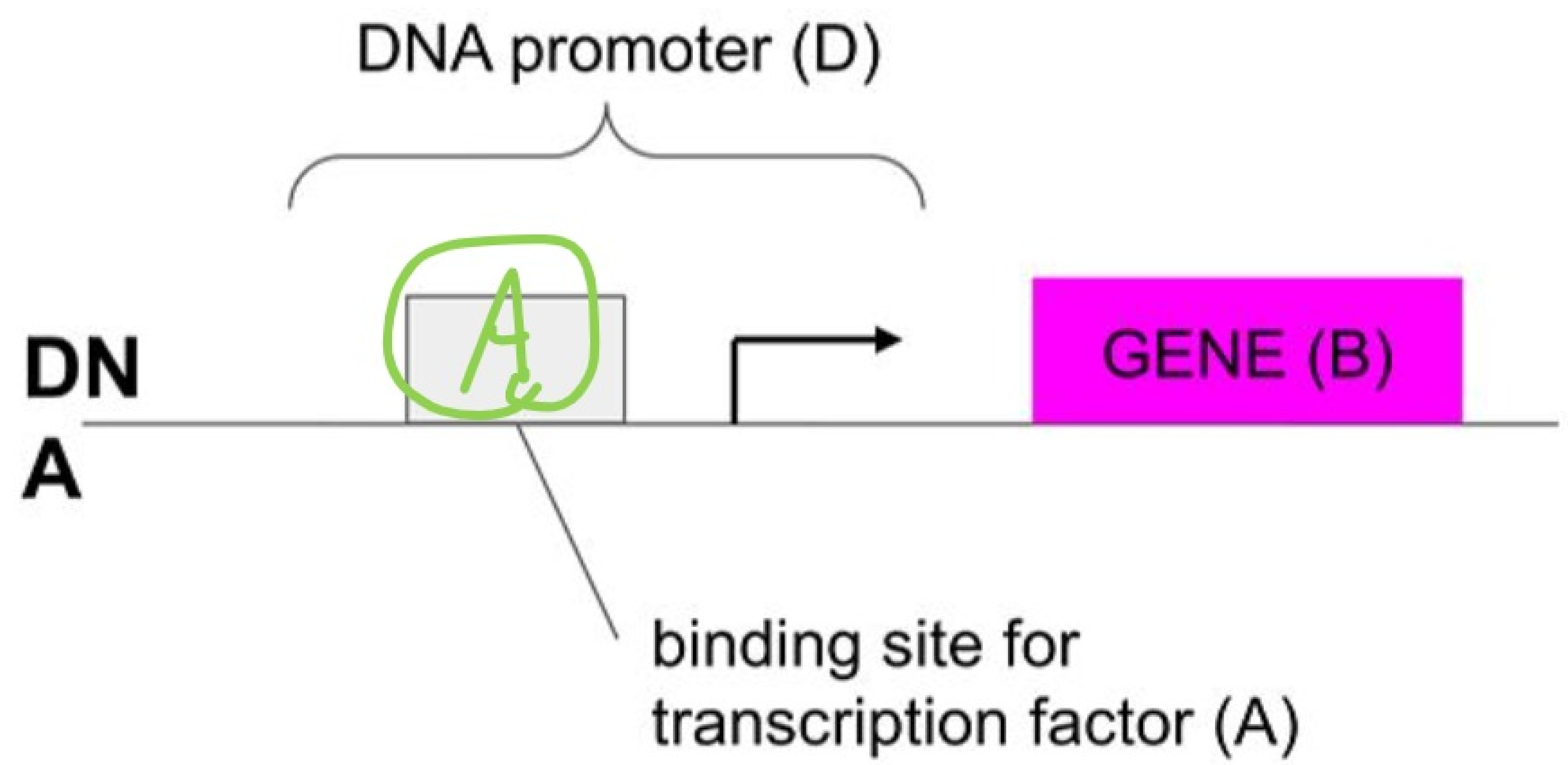
Bifurcation Graph

$$m^* = \frac{\alpha}{\delta}$$

$$\frac{dm}{dt} = \alpha - \delta m$$

Transcriptional Activation

- Transcription factor A **activates** Gene B
- How does this affect the production term?
- Use mass action kinetics to solve!



$$A \rightarrow B$$

$$\frac{dB}{dt} = \boxed{???} - \delta B$$

Transcriptional Activation

production term

$$D + A \underset{K_{off}}{\overset{K_{on}}{\rightleftharpoons}} [DA] \xrightarrow{K_t} D + A + B \longrightarrow \frac{dB}{dt} = K_t[DA]$$

quasi steady state

$$\frac{K_{on}}{K_{off}} = \frac{[DA]}{D \cdot A}$$

$$K_{on} DA = K_{off}[DA]$$

$$K = \frac{K_{off}}{K_{on}}$$

dissociation constant

bound or unbound

$$D_T = D + [DA]$$

$$D = D_T - [DA]$$

~~~ math magic ~~~

$$\boxed{f(A) = \frac{\beta A}{K + A}}$$

$[DA] = \ldots\ldots$

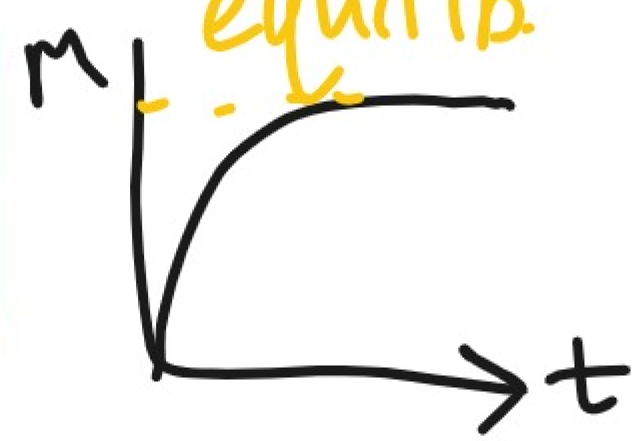
$$K_{on}(D_T - [DA])A = K_{off}[DA]$$

$$[DA] = \frac{K_{on} D_T A}{K_{off} + K_{on} A} \cdot \frac{1/K_{on}}{1/K_{on}}$$

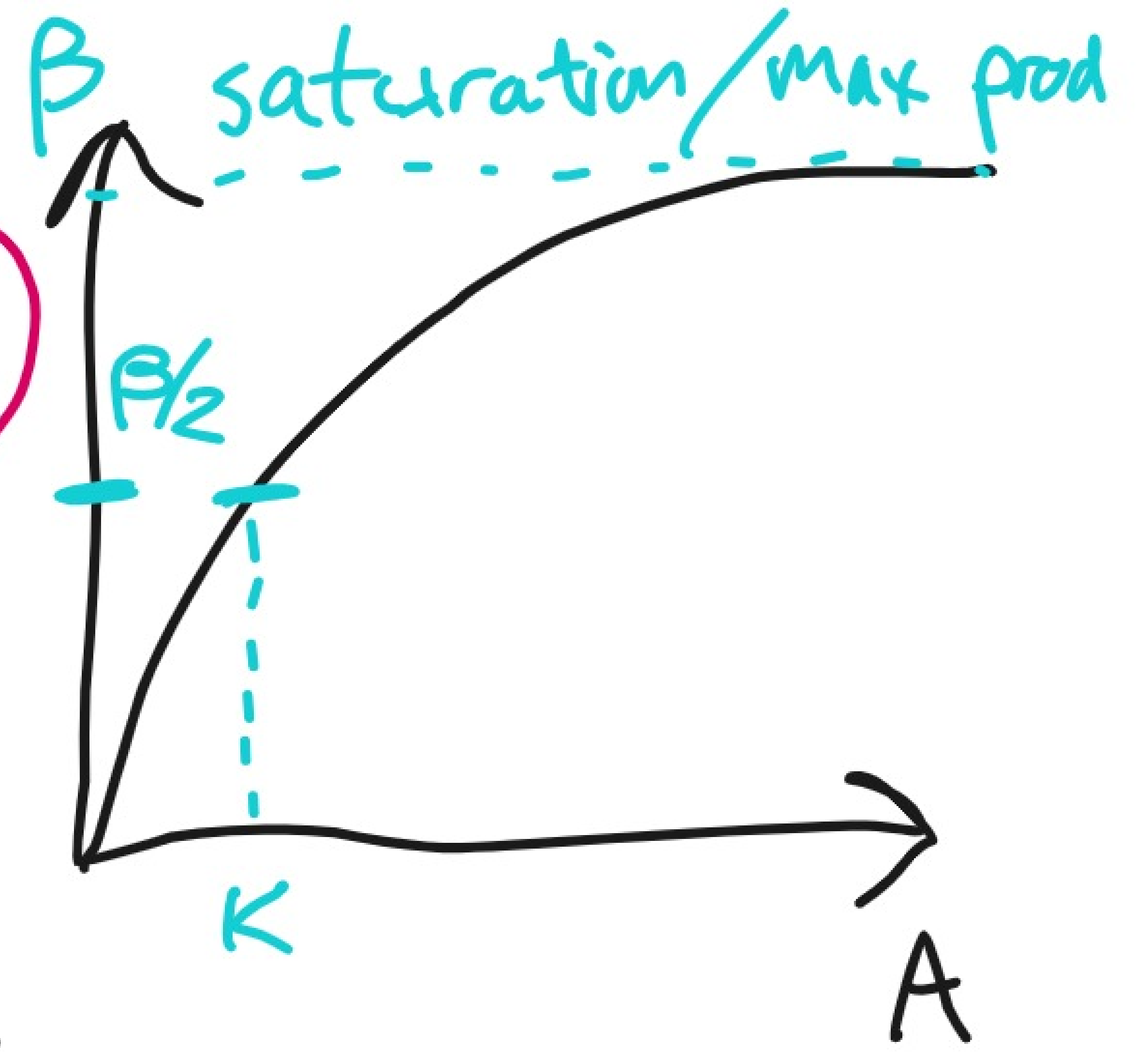
$$[DA] = \frac{\cancel{K_{on}} D_T A}{\frac{K_{off}}{K_{on}} + \cancel{K_{on}} A} \cdot \frac{1/K_{on}}{1/K_{on}}$$

$$[DA] = \frac{D_T A}{\underbrace{\frac{K_{off}}{K_{on}}}_{K_D} + A} = \frac{D_T A}{K_D + A}$$

$$\frac{dB}{dt} = K_t[DA] = \frac{\overbrace{K_t D_T}^{\beta} A}{K_D + A} = \frac{\beta A}{K_D + A} = \frac{dB}{dt}$$



prod $\frac{\beta A}{K + A}$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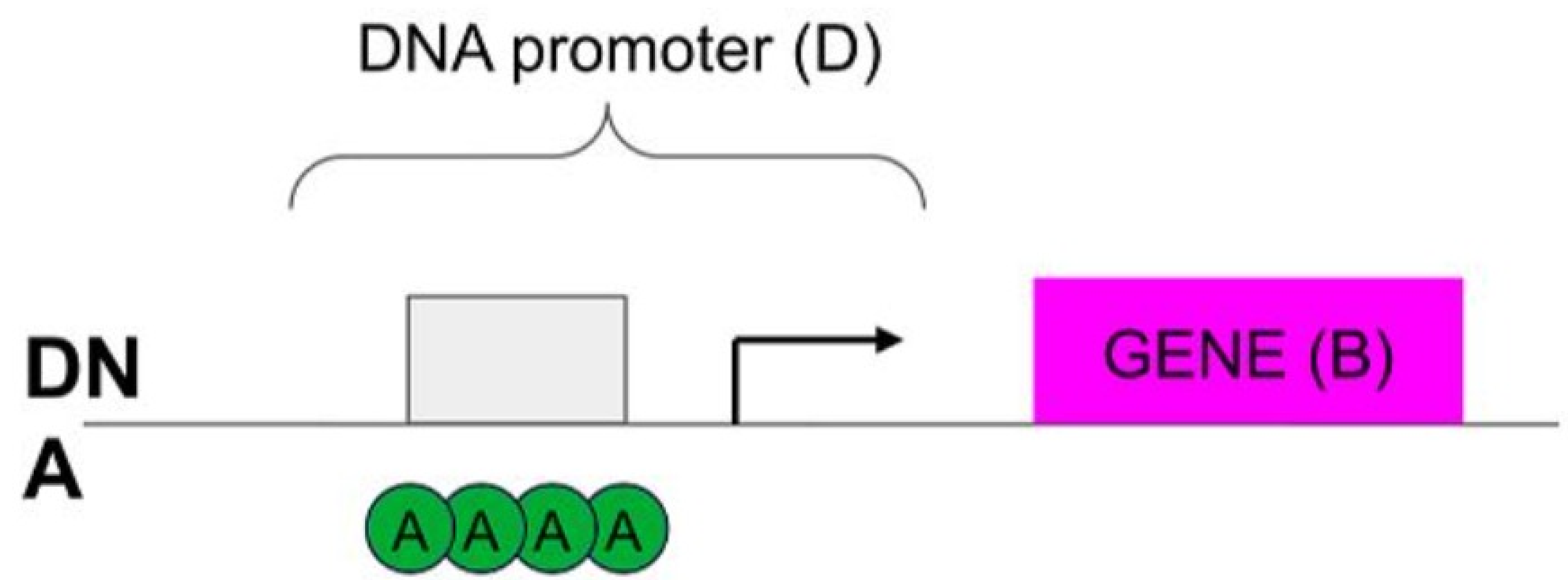
Cooperativity

- Multiple transcription factors bind together
- Dimer, trimer, … , n-mer
- Adds non-linearity to system



$$D + nA \rightleftharpoons [DA_n]$$

$$K^n[DA] = DA^n \qquad \boxed{K^n = \frac{K_{off}^{\,n}}{K_{on}^{\,n}}}$$

$$\frac{[DA]}{D_T} = \frac{A^n}{K^n + A^n}$$

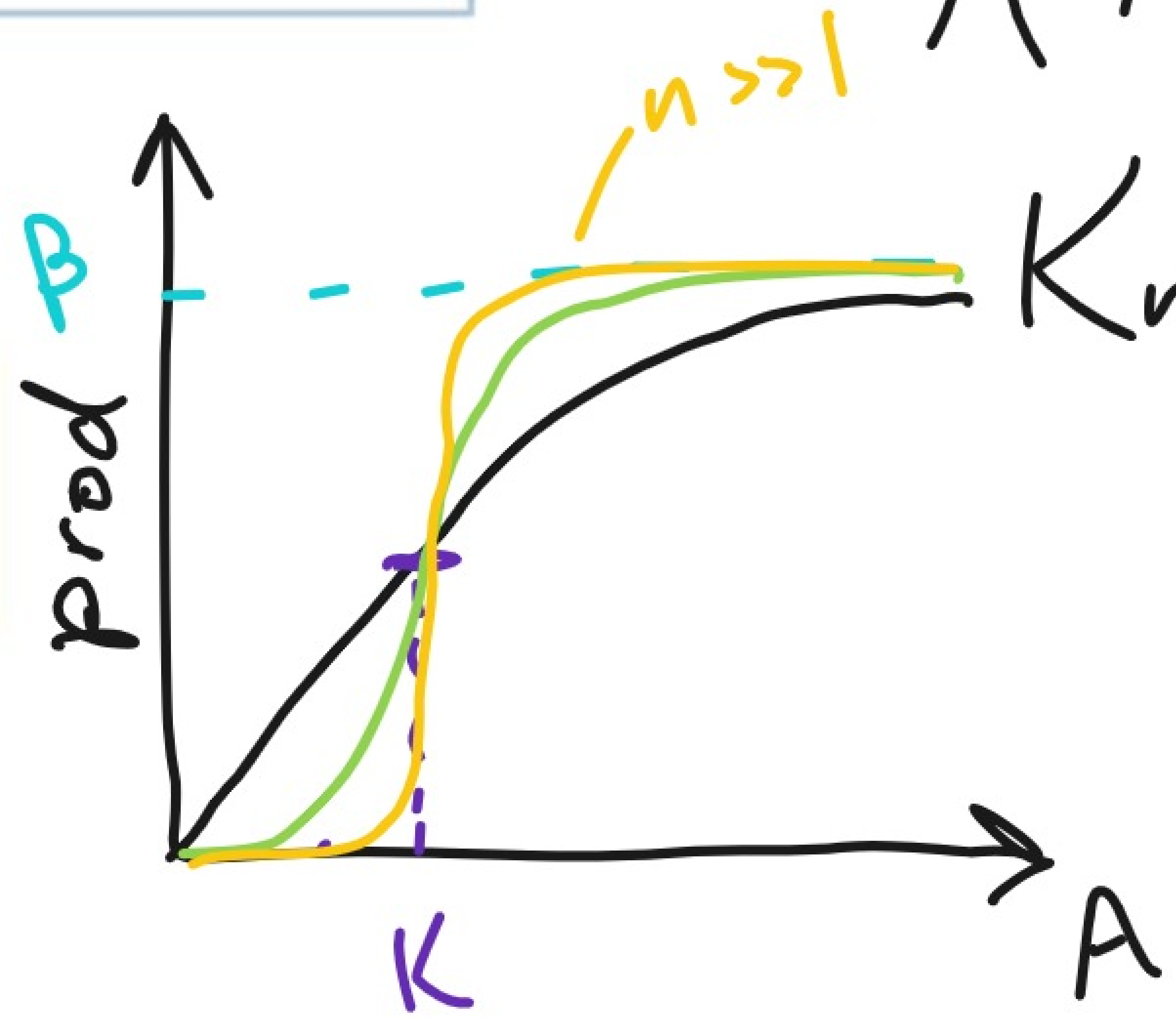
$$\boxed{f(A) = \frac{\beta A^n}{K^n + A^n}}$$

$$\frac{\beta A}{K + A}$$

$$A + A + A + A \cdots \xrightarrow{K_n} A_n$$

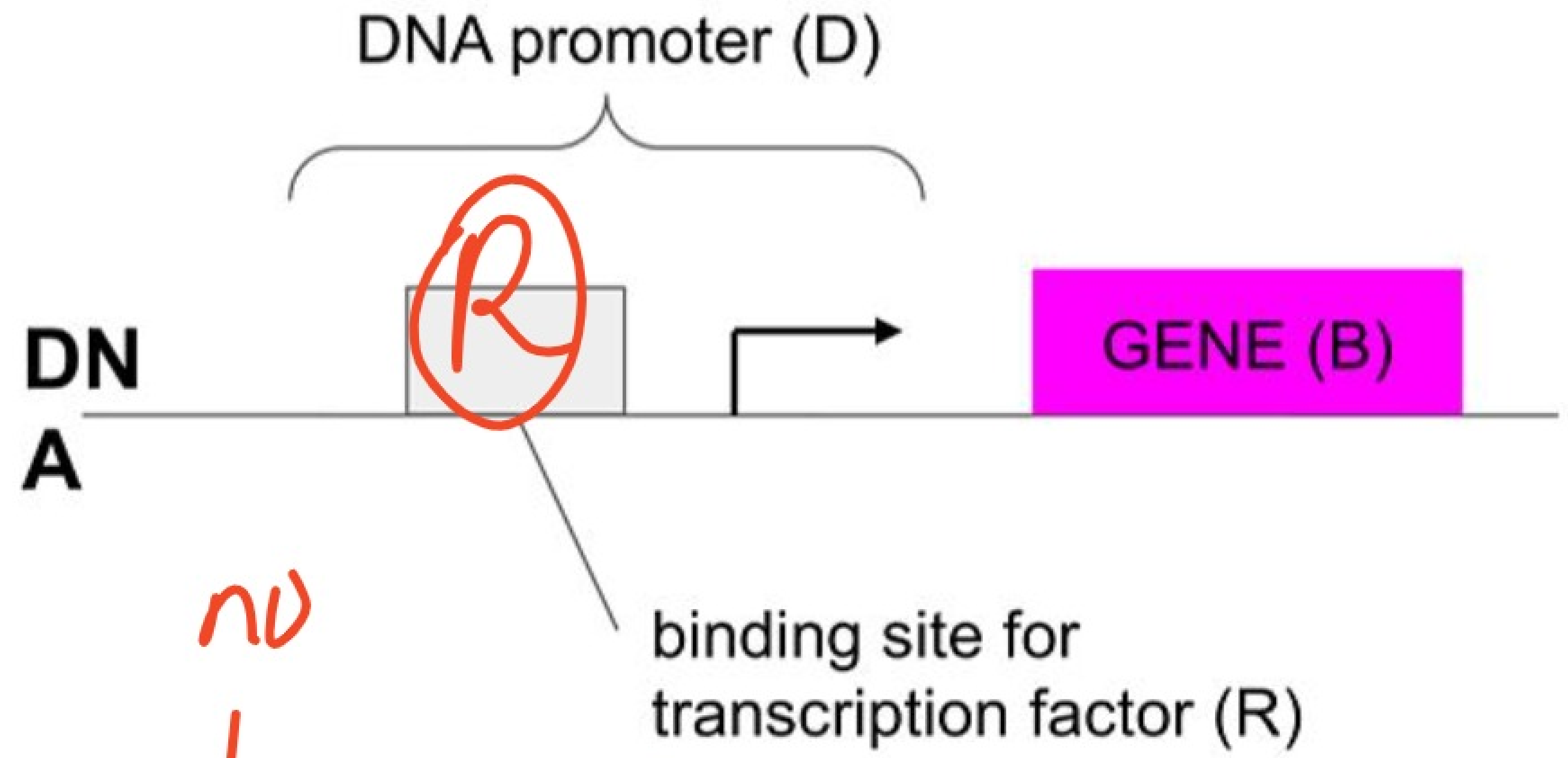
$$A + A \xrightarrow{K} A_2 + A \xrightarrow{K} A_3$$

$$K_n = K \cdot K \cdot \ldots \cdot K \cdot K = K^n$$



Transcriptional Repression

- Transcription factor R **represses** Gene B
- How does this affect the production term?
- Solve in a similar way to activation!



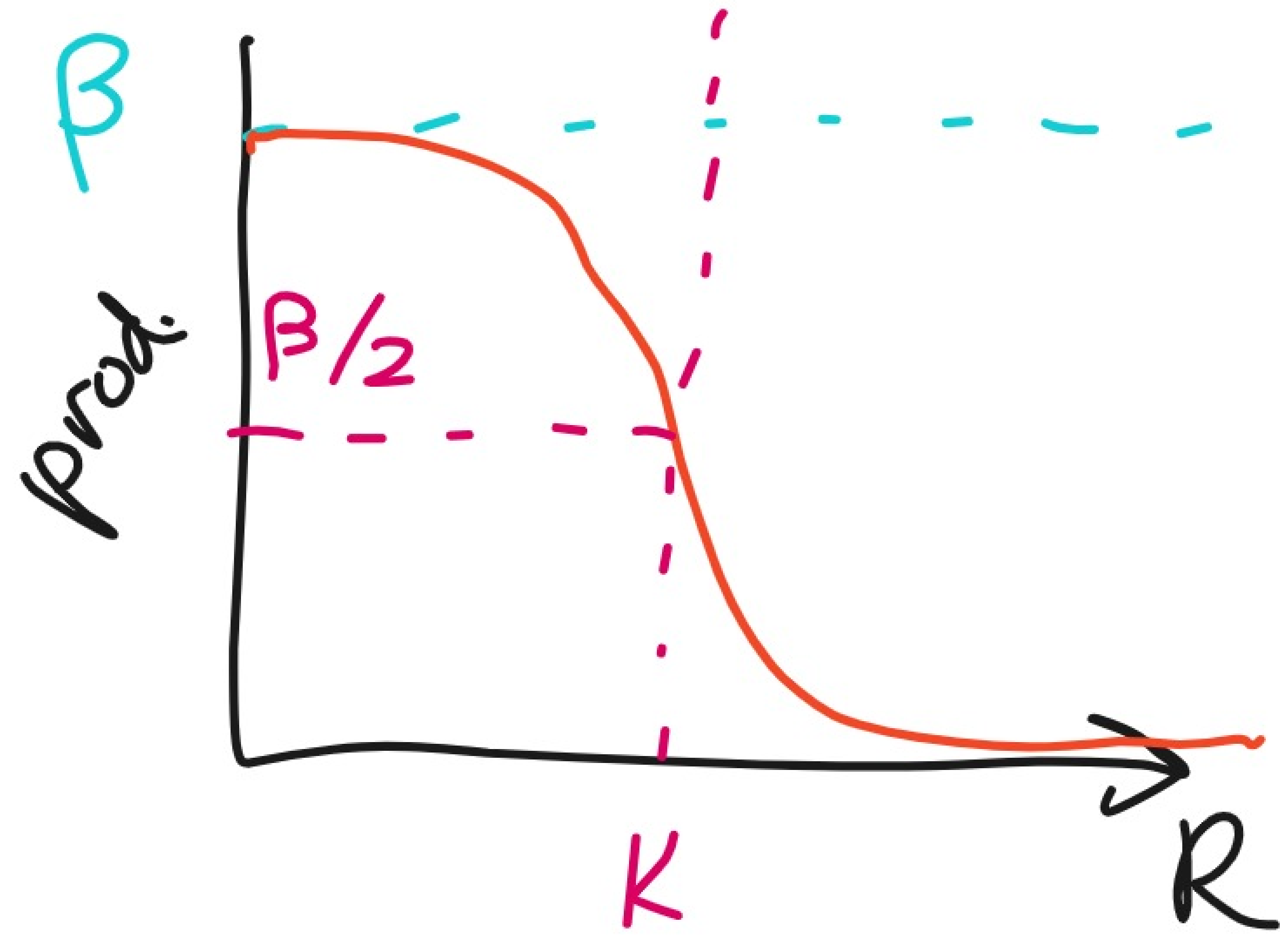
no transcription

$$R \to B \qquad \frac{dB}{dt} = \boxed{???} - \delta B$$

$$\boxed{f(A) = \frac{\beta}{1 + (\frac{R}{K})^n}}$$

$$\boxed{f(A) = \frac{\beta K^n}{K^n + R^n}}$$

$$\frac{\beta A^n}{K^n + A^n}$$



A

$$\frac{dA}{dt} = \frac{\beta K^n}{K^n + A^n} - \delta A$$

Repression (Self)
Negative Feedback

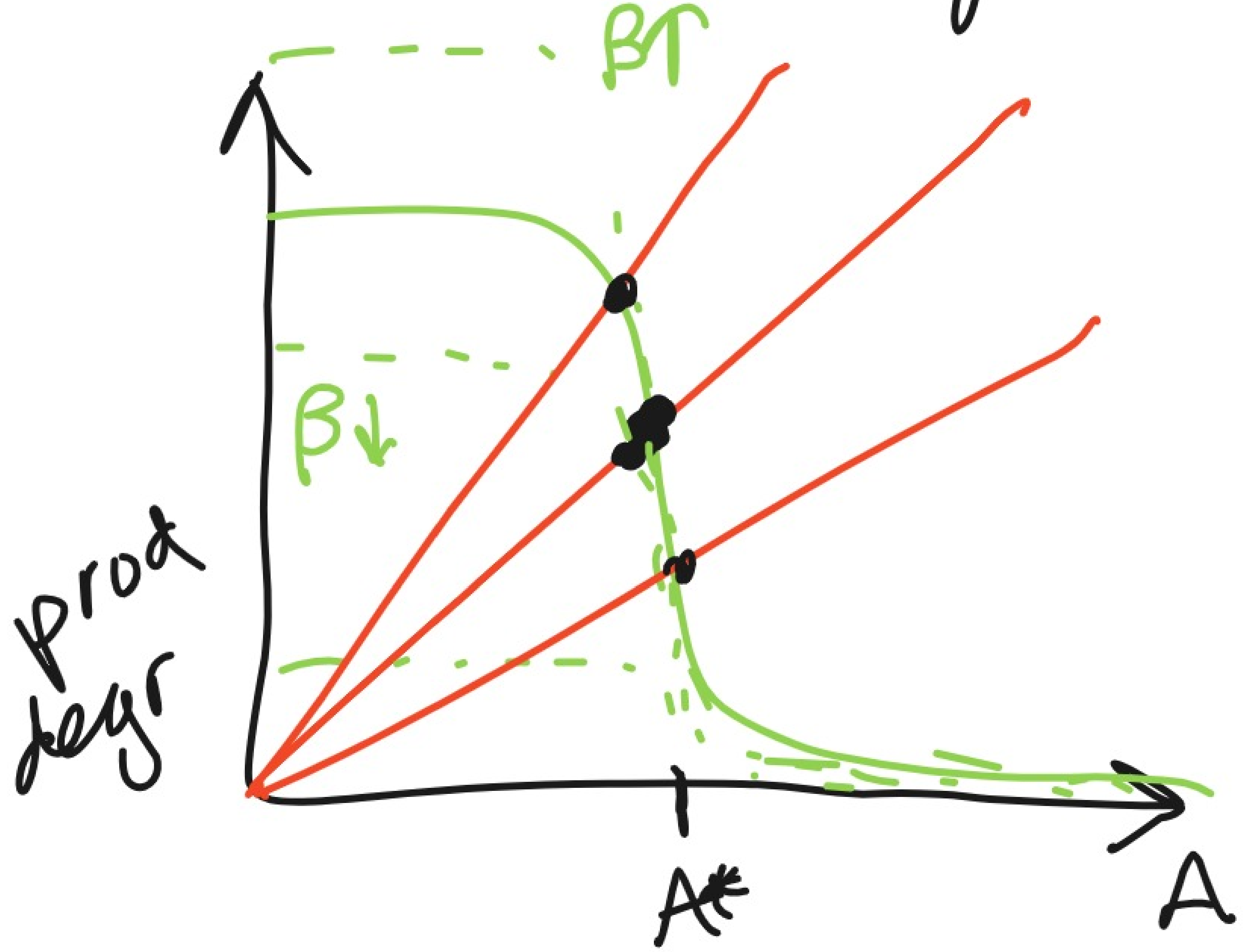
What is steady state?
How fast to reach steady state?

at steady state,

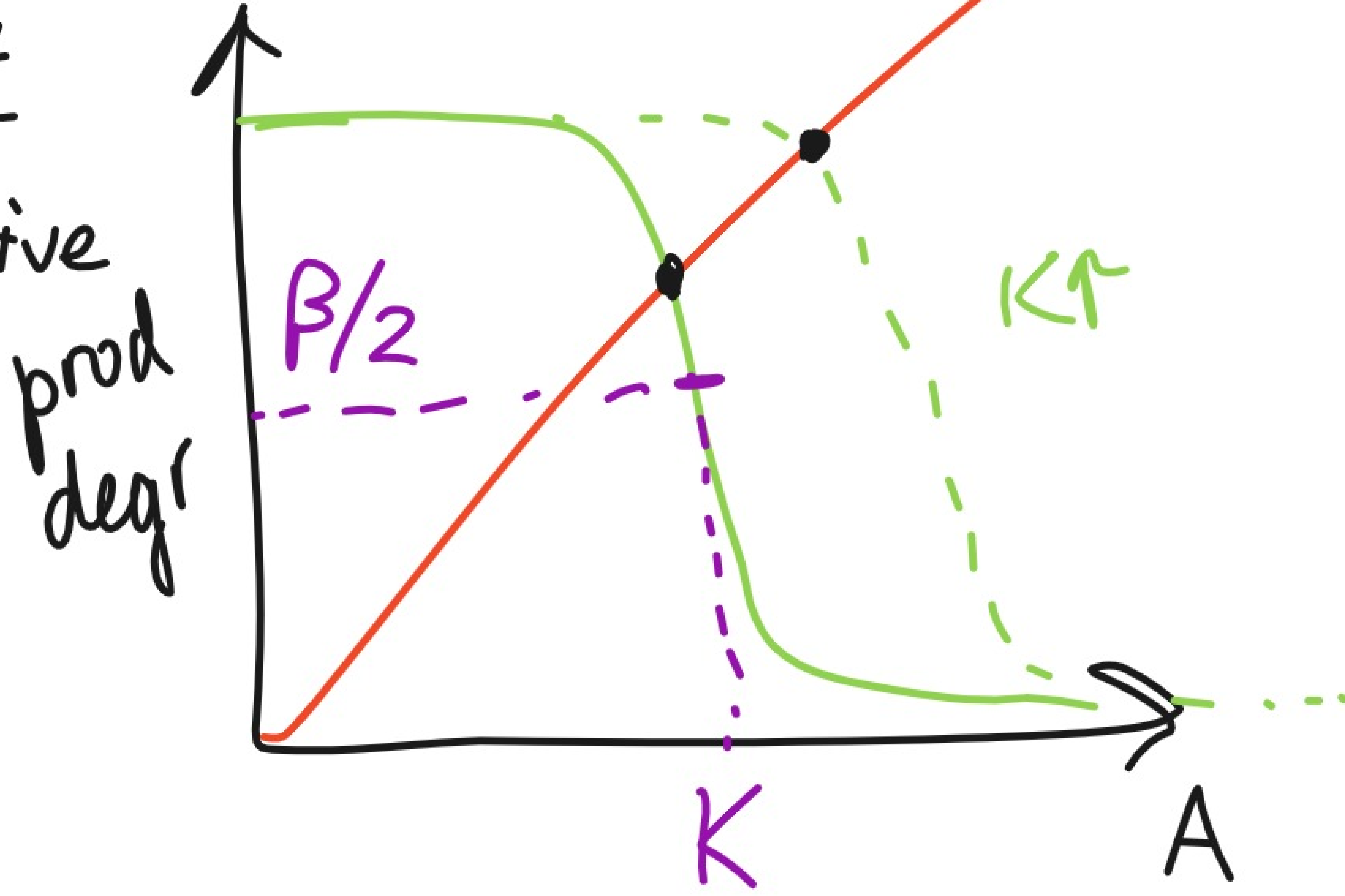
$$\frac{dA}{dt} = 0$$

Phase Line! (for SS)

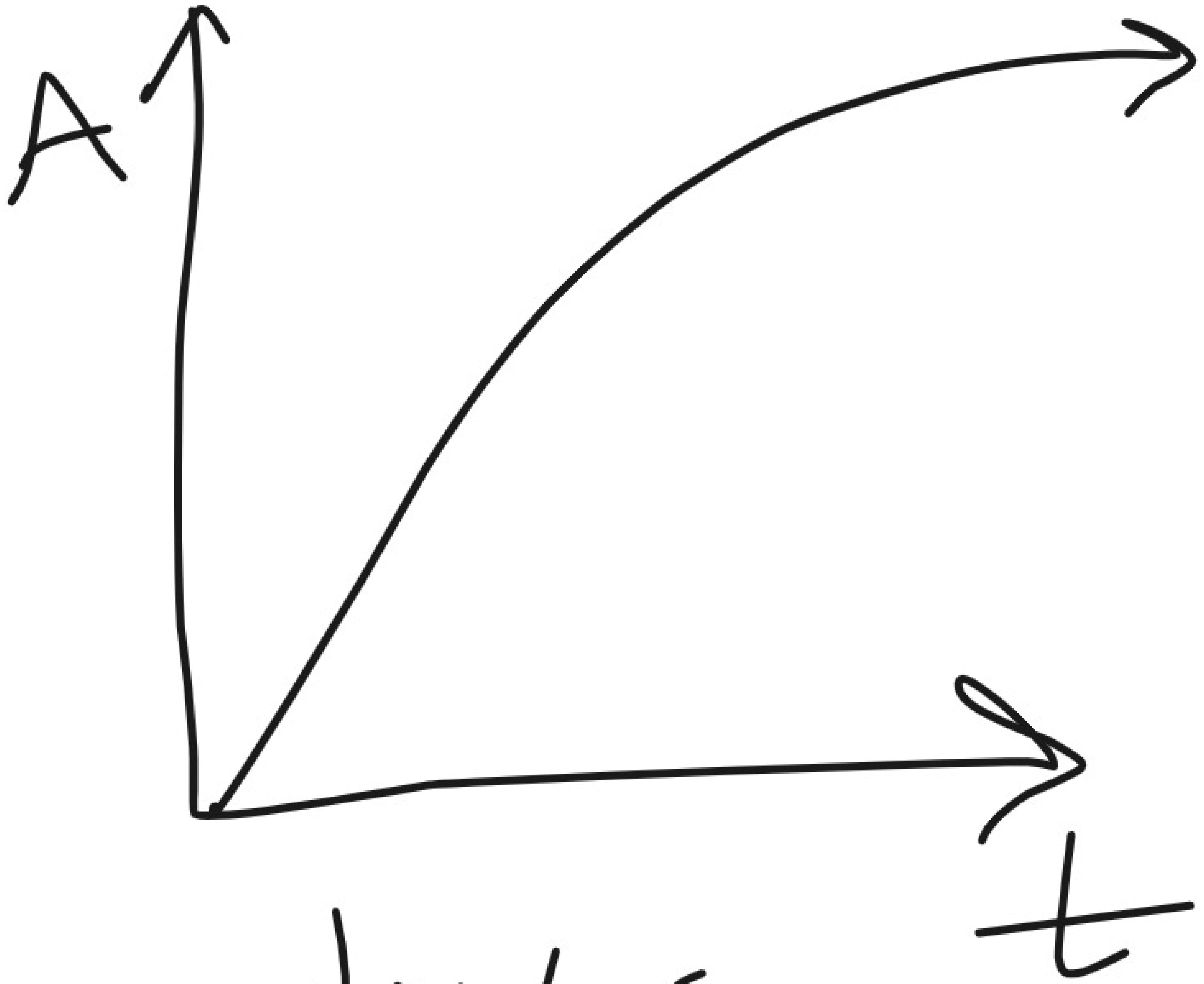
analytical SS impossible!



β? SS Robust
K? SS Sensitive
n? SS Robust
δ? SS Robust

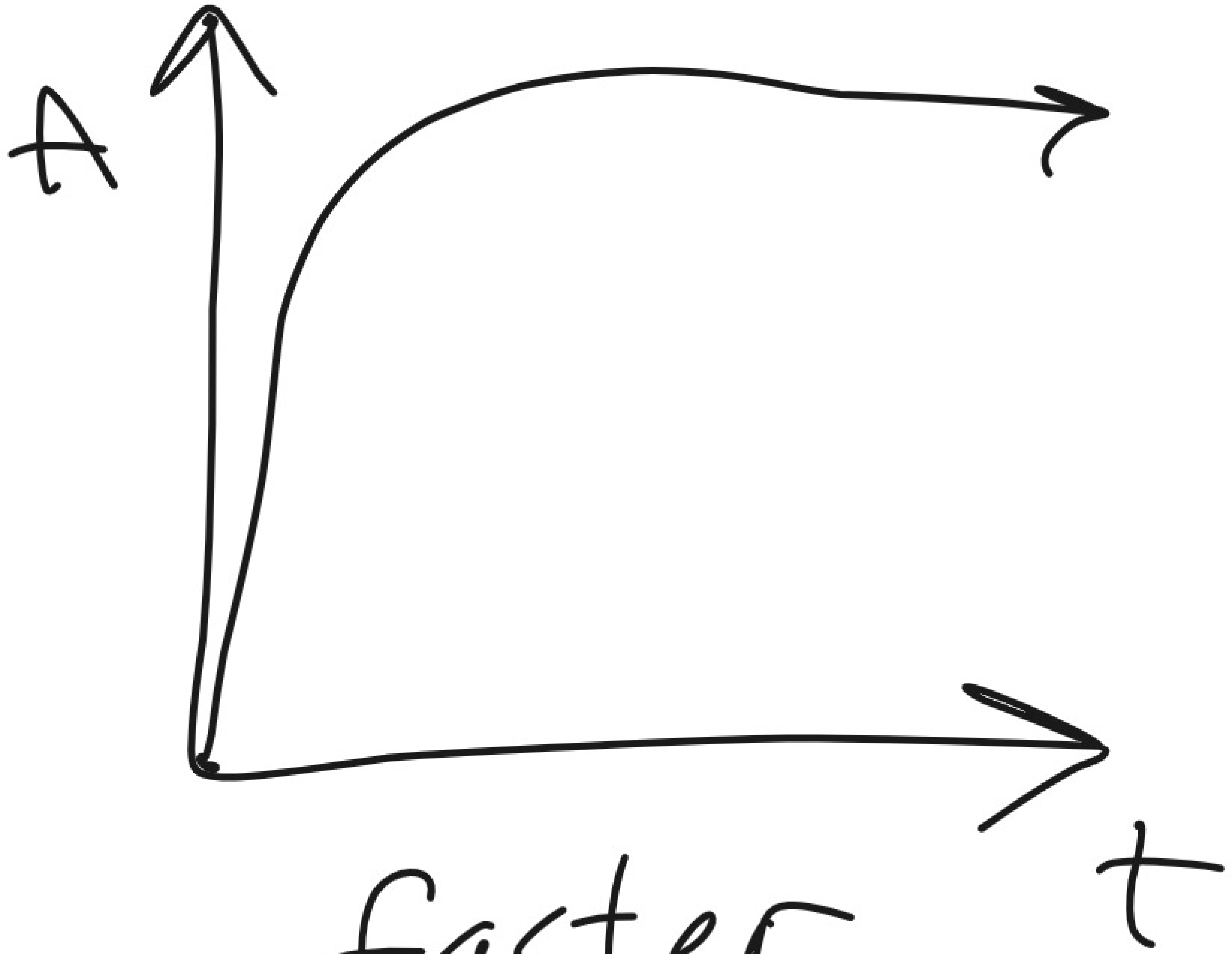


constant



slower

neg. feed



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