A background image showing a dense population of yeast cells, likely Saccharomyces cerevisiae, under a microscope. The cells are oval-shaped and appear to be in various stages of growth and division. The image is in grayscale and has a slightly blurred, artistic quality.

# **Mathematical Model of Nitrogen Metabolism in Yeast**

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# Outline

- **Modeling with Yeast**
- **Model**
  - Define all state variables, terms, and parameters involved in the system of differential equations
  - Analysis of steady-state
  - Simulation of dynamics
- **Model in relation with articles**

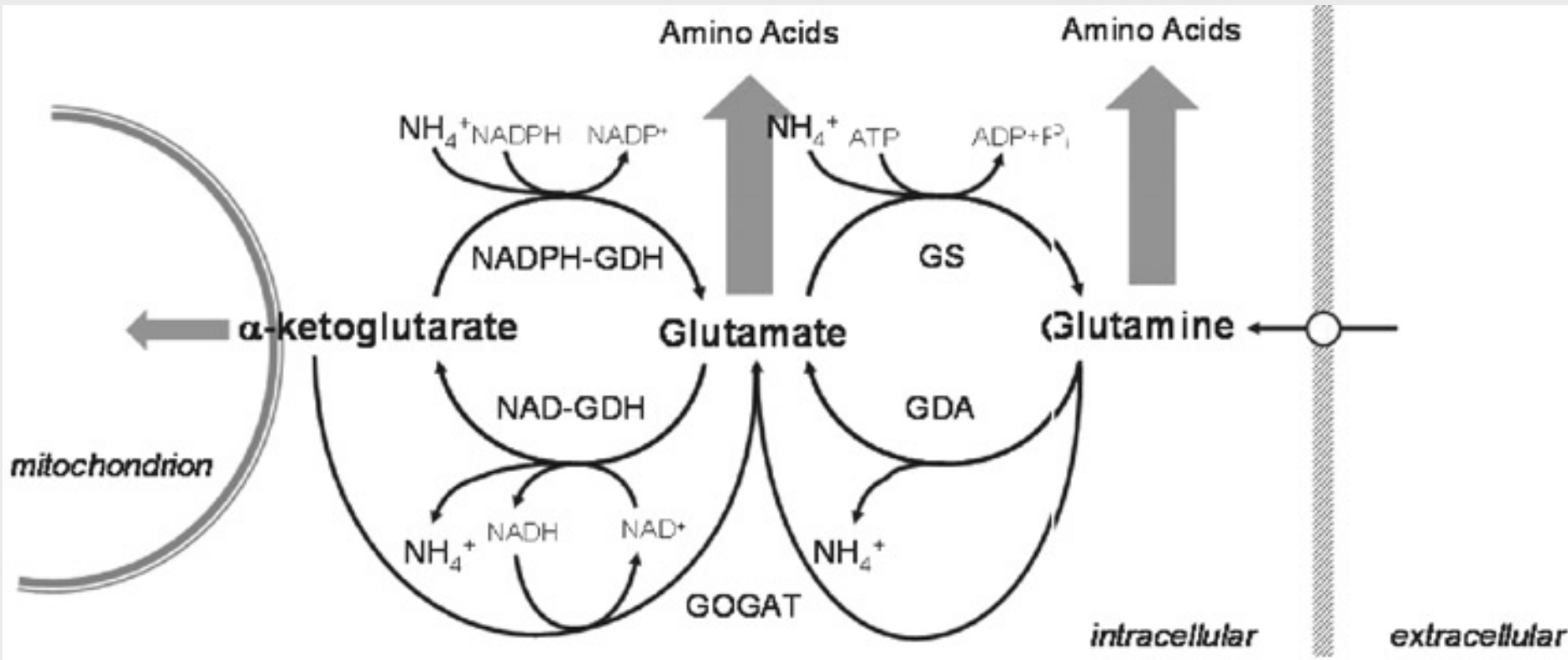
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# Background

- The article “The Concentration of Ammonia Regulates Nitrogen Metabolism in *Saccharomyces cerevisiae*” provides numerous models outlining the **effects that changes in ammonia concentration have on the nitrogen metabolism of yeast.**
- To build a better understanding of these processes, a model was created off of a list of equations gathered from existing data. The models were then compared to those featured in the paper described above.
- The article “Nitrogen regulated transcription and enzyme activities in continuous cultures of *Saccharomyces cerevisiae*” provides additional information on the **activities of yeast in continuous cultures of difference dilution rates under nitrogen limitation.**
- This article studied the changes in carbon and nitrogen fluxes under such environments and the effect different dilution rates had on transcription and nitrogen regulating genes.

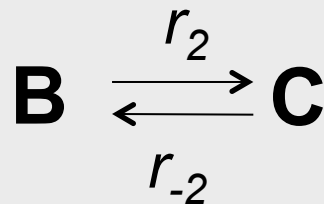
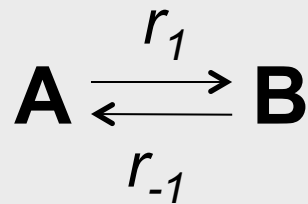
# Central Nitrogen Metabolism Pathway



# Outline

- Modeling with Yeast
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# Differential Equations and Variables



## State Variables

$a$  =  $\alpha$ -ketogluterate

$b$  = glutamate

$c$  = glutamine

## System of differential equations

$$\frac{da}{dt} = -r_1 a + r_{-1} b - r_3 a c$$

$$\frac{db}{dt} = r_1 a - r_{-1} b + r_{-2} c - r_2 b + 2r_3 a c$$

$$\frac{dc}{dt} = -r_{-2} c + r_2 b - r_3 a c$$

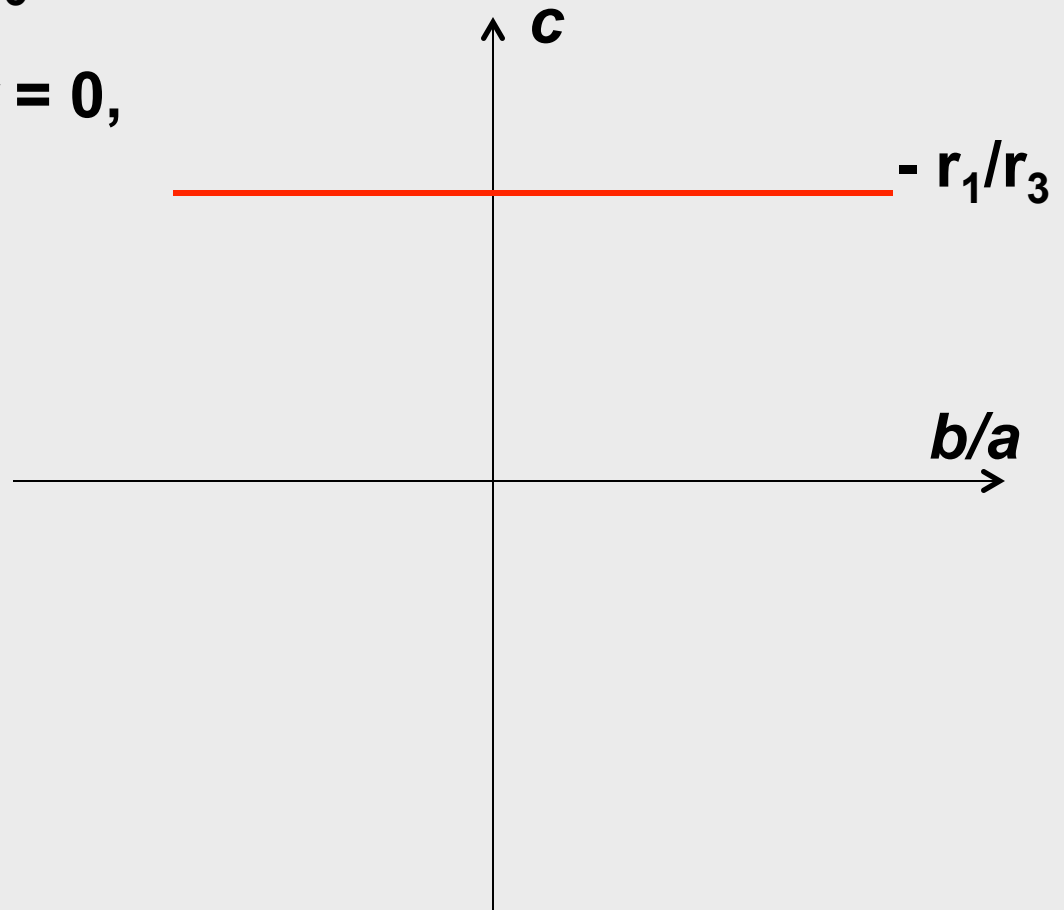
# Steady-state Analysis

At  $da/dt = 0$ , if  $b = 0$

$$c = (r_{-1}b / r_3a) - r_1/r_3$$

At  $db/dt = 0$  and  $dc/dt = 0$ ,

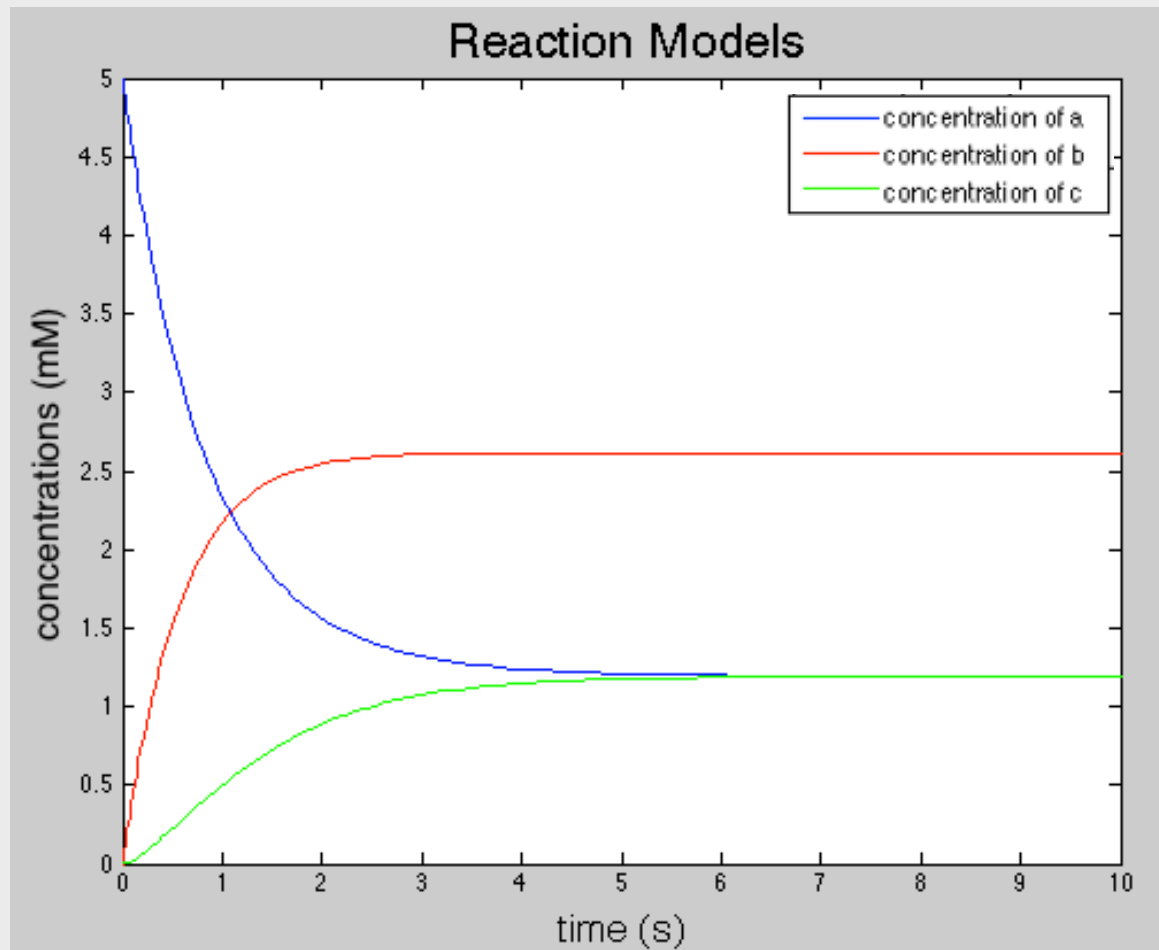
$$c = r_2b / (r_{-2} + r_3a)$$



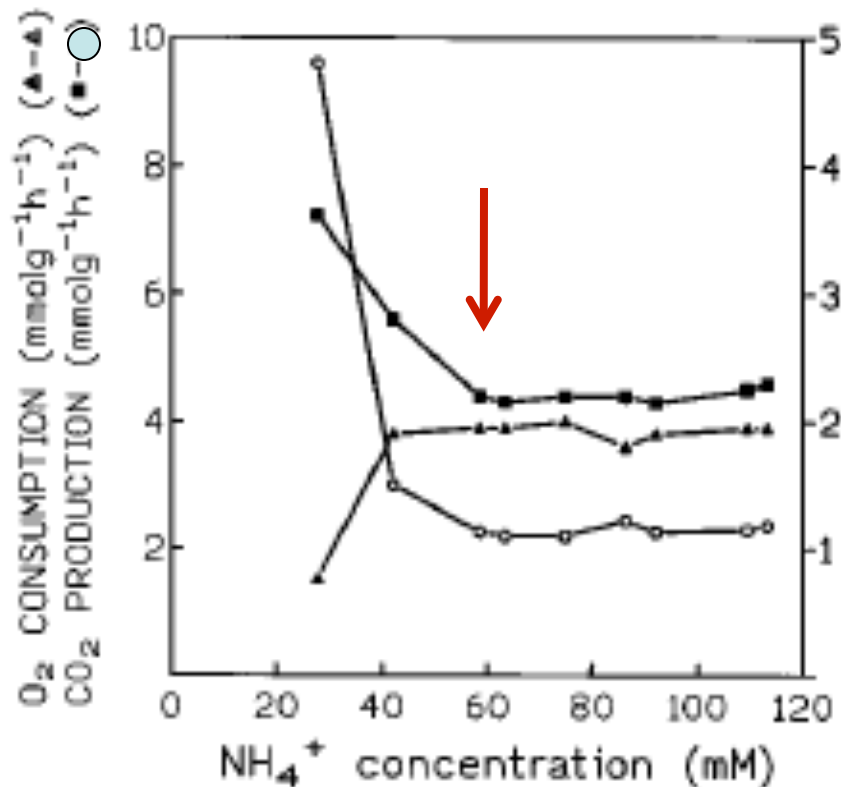


# Graphical Output of the Dynamic's Simulation

All parameters equal to 1



# When the Culture Was Switched from Ammonium Limitation to Ammonium Excess, No Further Changes in Respiratory Quotient Were Observed

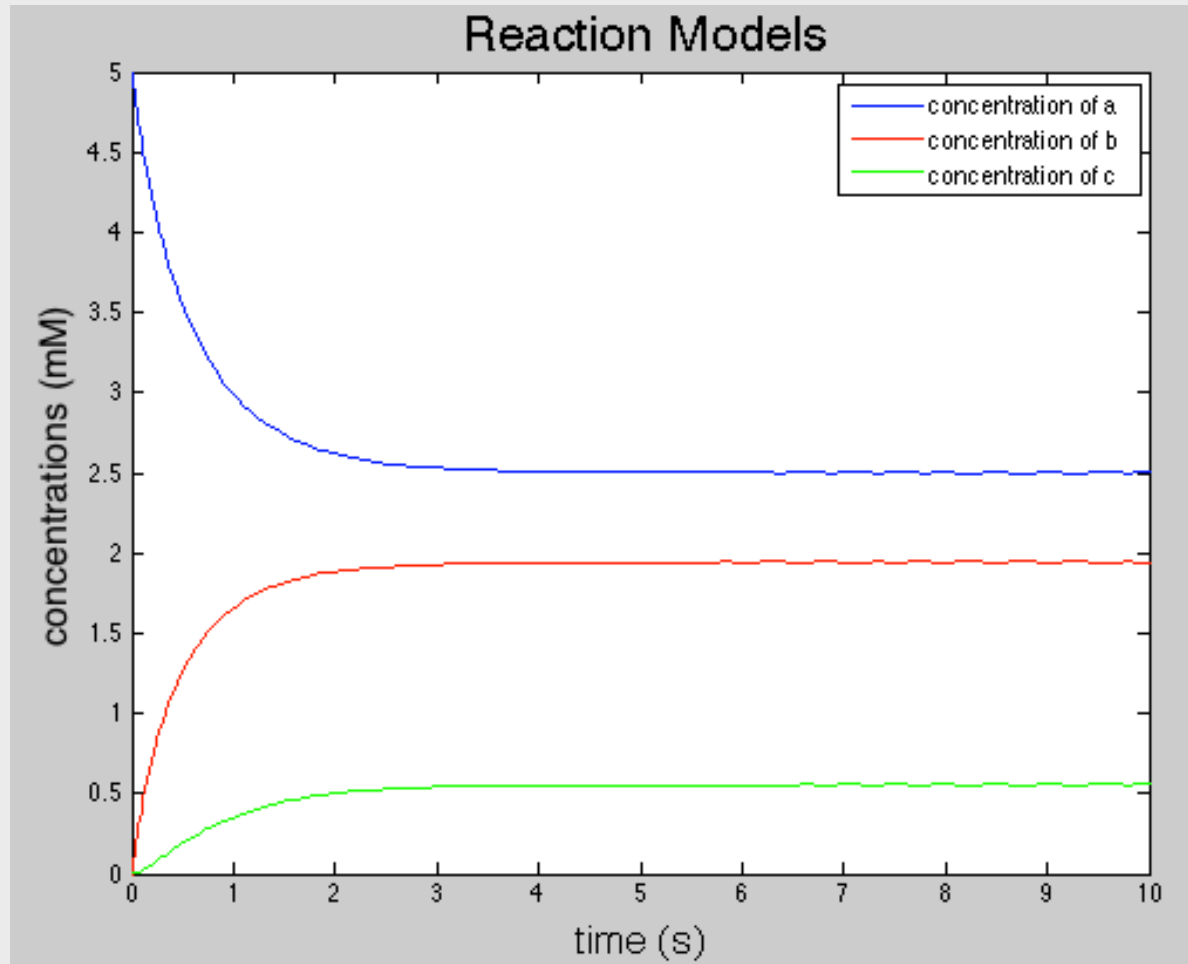


- The “respiratory quotient” shows whether the culture is performing fermentation or respiration.
- At 29 mM NH<sub>4</sub><sup>+</sup> in the feed, the culture is performing fermentation.
- Beginning at 44 mM NH<sub>4</sub><sup>+</sup>, the culture switches over to respiration.
- After 61 mM NH<sub>4</sub><sup>+</sup> (excess), no further changes in carbon metabolism are observed.

$$\text{respiratory quotient} = \text{CO}_2 \text{ produced} / \text{O}_2 \text{ consumed}$$

# Modifying $r_{-1}$ parameter

Set  $r_{-1} = 2$



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# Discussion

"If the ammonia concentration is the regulator, this may imply that *S. cerevisiae* has an ammonia sensor which could be a two-component sensing system for nitrogen..."

- The two component system could be referring to the two step reaction that occurs in the yeast. The first component is the reaction transforming  $\alpha$ -ketoglutarate into glutamate and then the second component is the reaction transforming glutamate into glutamine.
- Before each component, the nitrogen concentration must be evaluated before proceeding with the reaction. Therefore, an ammonia sensor would have to remain sensitive to both instances.
- The concept of two components could also be referring to the extracellular and intracellular concentrations of nitrogen, which both provide a unique measure. For the hypothetical ammonia sensor to run, both concentrations must be considered.

# Summary

- **Modeling with Yeast**
- **Model**
  - **State variables**
  - **System of Differential Equations**
  - **Terms**
  - **Parameters**
  - **Analysis of steady-state**
  - **Simulation of dynamics with graphical output**
- **Model in relation with articles**

# Work Cited

- **ter Schure, E.G., Sillje, H.H.W., Verkleij, A.J., Boonstra, J., and Verrips, C.T. (1995) *Journal of Bacteriology* 177: 6672-6675.**
- **Schure, E. G. Ter, H. H. W. Sillje, L. J. R. M. Raeven, J. Boonstra, A. J. Verkleij, and C. T. Verrips. (1995) *Microbiology* 141.5: 1101-108.**