MSc Computational Science
joint programme UvA/VU

MODELLING DIFFUSIVE SIGNALLING IN *ASPERGILLUS* SPP. GERMINATION INHIBITION

INTERMEDIATE PRESENTATION - MAY

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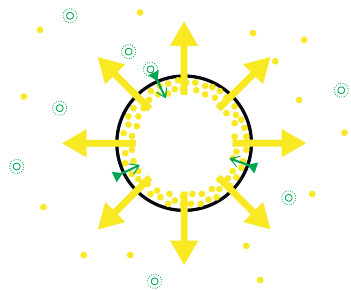
OUTLINE

INTRODUCTION

Considerations for parameter fitting

- There are **two germination-determining mechanisms**:
  - auto-inhibition
  - carbon sensing
- We have a model proposal for the **auto-inhibition**.
- But the germination rate is also influenced by **carbon sensing**.
- **Parameter fitting on germination rate data** requires the germination probability to be expressed in terms of both processes.



INTRODUCTION

Inducer assumptions

- Carbon sources (glucose, amino acids) are **germination inducers** that bind to receptors in the cell wall.
- Experiments have shown that pyrene [3] and 1-octen-3-ol [2] can easily pass through the hydrophobin layer, but these are **much more hydrophobic** molecules than glucose (positive $\log K$).

carbon source	$\log K$
glucose	-3.2
arginine	-3.88
proline	-2.55
alanine	-0.6

Table: Octanol-water partition coefficient of different carbon sources.

- Therefore, the rodlet layer **possibly slows down** the access of carbon signals to the receptor proteins.

INTRODUCTION

Inducer assumptions

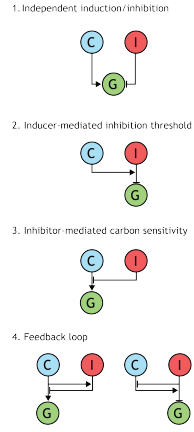
- Carbon signals are received by **G-proteins** and **RasA** proteins, which are potentially linked to the activation of the cAMP-PKA pathway upon break of dormancy.
- These proteins are usually membrane-bound but can extend into the inner cell wall polysaccharide layer.
- Despite their slower intake, the signal thresholds for activating the germination regime may be relatively low.

OUTLINE

INDUCER-INHIBITOR INTERACTIONS

Independent induction/inhibition

- The following types of interactions are possible:
  - Independent induction/inhibition
  - Inducer-modulated inhibition
    - Inducer shifts inhibition threshold (1)
    - Inducer increases inhibitor permeation (2)
  - Inhibitor-modulated carbon sensitivity
    - Inhibitor attenuates signal strength (3)
    - Inhibitor shifts signal threshold (4)
  - Feedback loop
    - (1) and (3)
    - (1) and (4)
    - (2) and (3)
    - (2) and (4)



INDUCER-INHIBITOR INTERACTIONS

Independent induction/inhibition

- In the simplest scenario, the two mechanisms can be viewed as **mutually independent**, causing germination when both conditions are fulfilled simultaneously:

$$c_{\text{in}} < c_T \quad \text{and} \quad sc_{\text{cs}} > s_T, \tag{1}$$

- Like the inhibition threshold, the induction threshold s_T can be modelled by a normally distributed random variable ω.
- Since the inducer concentrations do not vary in the experiments of interest, c_{cs} can be absorbed into the signal strength s.
- The combined germination probability is

$$P(\beta < \gamma \cap \omega < s) = \Phi\left(\frac{s-\mu_\omega}{\sigma_\omega}\right) \int_0^\infty \left[1 - \Phi\left(\frac{\beta(\xi)-\mu_\gamma}{\sigma_\gamma}\right)\right] \frac{1}{\sqrt{2\pi}\sigma_\xi} \exp\left(-\frac{(\xi-\mu_\xi)^2}{2\sigma_\xi^2}\right) d\xi. \tag{2}$$

INDUCER-INHIBITOR INTERACTIONS

Inducer-modulated inhibition threshold

- In a different scenario, the germination starts solely upon depletion of the inhibitor, but **the inducer raises or lowers the threshold** at which the inhibitor is considered depleted.
- As derived previously, the germination probability is

$$P(\beta(\xi) < \gamma) = \int_0^\infty \left[1 - \Phi\left(\frac{\beta(\xi) - \mu_\gamma}{\sigma_\gamma}\right)\right] \frac{1}{\sqrt{2\pi}\sigma_\xi} \exp\left(-\frac{(\xi - \mu_\xi)^2}{2\sigma_\xi^2}\right) d\xi, \tag{3}$$

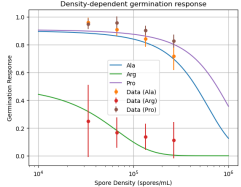
where γ is a normally distributed random variable proportional to the signalling strength.

INDUCER-INHIBITOR INTERACTIONS

Inducer-modulated inhibition threshold

» Fitting this model to experimental data [1] yields

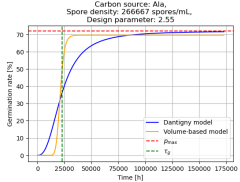
inducer	P_{eff}	μ_γ	σ_γ
Ala	$4.4 \times 10^{-8}\,\text{cm}\,\text{s}^{-1}$	$3.655\,72 \times 10^{-5}$	$2.847\,91 \times 10^{-5}$
Arg	$1.99 \times 10^{-8}\,\text{cm}\,\text{s}^{-1}$	$1.033\,01 \times 10^{-20}$	$6.230\,48 \times 10^{-5}$
Pro	$6.36 \times 10^{-8}\,\text{cm}\,\text{s}^{-1}$	$6.077\,02 \times 10^{-5}$	$4.570\,27 \times 10^{-5}$



» The model fit is relatively aligned with the data and resembles the **time-dependent Dantigny curve**, but with a much steeper onset.

» Here we assume that the carbon signal strength is **constant over time**.

» The permeation constant changes slightly, so **permeation might be affected by the inducer** as well.



INDUCER-INHIBITOR INTERACTIONS

Inhibitor-modulated carbon sensitivity

- Another possibility is that the **inhibitor suppresses the carbon signalling pathway**, which determines germination.
- Once the inhibition is removed through diffusion, the cAMP-PKA pathway may receive stronger triggers that can switch the germination regime on.
- The inhibitor may act on the carbon signalling pathway by
  - attenuating the signal strength,
  - shifting the signal threshold.

INDUCER-INHIBITOR INTERACTIONS

Inhibitor-modulated carbon sensitivity - **signal attenuation**

- The inhibitor may attenuate the carbon signal strength by a Hill-type factor:

$$s(c_{\text{in}}) = s_{\max} \frac{1}{1 + \left(\frac{c_{\text{in}}}{K_I}\right)^n}, \tag{4}$$

where K_I a half-saturation constant and n is a Hill exponent. The signal strength maximum, $s_{\max}$, can be considered constant for simplicity (the threshold absorbs the variation).

- The germination probability for a specific spore is thus

$$P(\omega < s \mid c_{\text{in}}) = \Phi\left(\frac{s(c_{\text{in}}) - \mu_\omega}{\sigma_\omega}\right). \tag{5}$$

INDUCER-INHIBITOR INTERACTIONS

Inhibitor-modulated carbon sensitivity - **signal attenuation**

- The two random variables in c_{in} are ξ and ψ. Therefore, the full CDF is

$$P(\omega < s) = \int_0^\infty \int_0^\infty \Phi\left(\frac{s_{\max}\left[1 + \left(\frac{c_{\text{in}}(\xi,\psi)}{K_I}\right)^n\right]^{-1} - \mu_\omega}{\sigma_\omega} \right) d\xi\, d\psi, \tag{6}$$

where

$$c_{\text{in}}(\xi,\psi) = \left[\phi + (1-\phi)e^{-\frac{t}{\tau(1-\phi)}}\right]\psi. \tag{7}$$

INDUCER-INHIBITOR INTERACTIONS

Inhibitor-modulated carbon sensitivity - **threshold shift**

- In the second case, the threshold is linearly shifted from a randomly fluctuating baseline ω_0 by a factor k:

$$\omega(c_{\text{in}}) = \omega_0 + kc_{\text{in}}. \tag{8}$$

- The condition for germination can then be rewritten from $s > \omega_0 + kc_{\text{in}}$ to $s - kc_{\text{in}} > \omega_0$.
- This yields the spore-specific germination probability:

$$P(\omega_0 < s - kc_{\text{in}} \mid c_{\text{in}}) = \Phi\left(\frac{s - kc_{\text{in}} - \mu_{\omega_0}}{\sigma_{\omega_0}}\right) \tag{9}$$

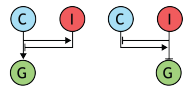
and the general probability

$$P(\omega < s) = \int_0^\infty \int_0^\infty \Phi\left(\frac{s - kc_{\text{in}} - \mu_{\omega_0}}{\sigma_{\omega_0}}\right) d\xi \, d\psi. \tag{10}$$

INDUCER-INHIBITOR INTERACTIONS

Feedback loop

- Finally, a scenario may exist in which the inhibitory mechanism and the signalling pathway are **mutually dependent**.
- For example, a **strengthened cAMP-PKA pathway** may gradually **lift the inhibition threshold**, while a **reduction in the inhibitor concentration** may **reinforce the carbon signalling**.
- The germination-determining threshold may either be dependent on carbon signal or on the depletion of the inhibitor.
- The ODEs for this systems are yet to be formulated.



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