Universität Bielefeld

Competition and coexistence in bacterial range expansion: the role of founder cells and spatial heterogeneities

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Lukas Eigentler

Biofilms

- Bacterial biofilms are surface-adhering multicellular collectives embedded in a self-produced extracellular matrix.
- Biofilms can have both beneficial and detrimental effects on the surrounding environment.
- Example: the soil-dwelling bacterium *Bacillus subtilis* forms biofilms on the roots of plants, where some strains promote the growth of plants.
- To fully realise their potential as biocontrol agents, strains need to be capable of coexisting with (or outcompeting) other biofilm-forming strains in the rhizosphere.
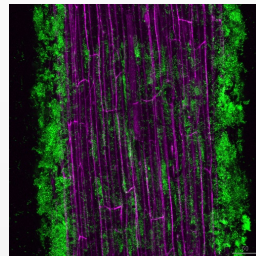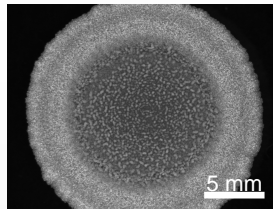
Competition within biofilms

- Competition in biofilms is underpinned by kin discrimination.
- Many mechanisms of kin discrimination require spatial co-location of strains.
- Take a step back: need to understand the role of spatial structure first.
- Often studied through the "colony biofilm model"[a]

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[a]Eigentler, L. et al.: *Open Biol.* 12.220294 (2022).
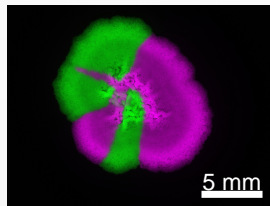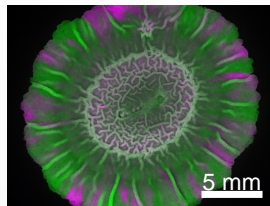
Competition within biofilms

- Spatial structure is best studied using isogenic strains: all other competitive mechanisms (e.g. kin discrimination) are excluded from the model system by design.
- Isogenic strains: Low founder densities promote spatial segregation and formation of spatial sectors.[1,2]
- Questions: How does spatial structure arise and how does it affect competitive interactions?

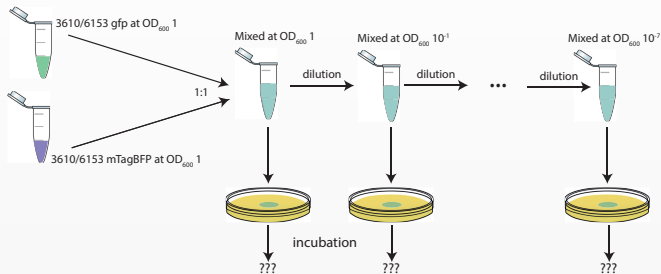5 mm

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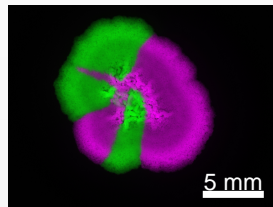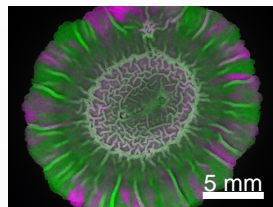
[1]van Gestel, J. et al.: *ISME J.* 8.10 (2014)
[2]Martinez-Garcia, R. et al.: *PLoS Comput. Biol.* 14.4 (2018)

Methods

Experimental assay:

Tested for

- *B. subtilis* NCIB3610 ("standard" lab strain).
- *B. subtilis* NRS6153 (isolated from garden soil in Tayport, Fife, UK).

Methods

Mathematical model for isogenic strain pair:

$$\frac{\partial B_1}{\partial t} = \nabla \cdot \left(\left(1 - (B_1 + B_2)\right) \nabla B_1 \right) + B_1 \left(1 - (B_1 + B_2)\right),$$

$$\frac{\partial B_2}{\partial t} = \nabla \cdot \left(\left(1 - (B_1 + B_2)\right) \nabla B_2 \right) + B_2 \left(1 - (B_1 + B_2)\right).$$

- Circular domain $\Omega = \{x \in \mathbb{R}^2 : \|x\| \leq R\}$.
- Logistic growth
- Diffusion with density-dependent diffusion coefficient, motivated by experimental observation that initially separated colonies abut rather than merge[1].

(c) 48 hrs
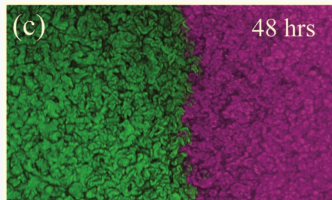

[1] Matoz-Fernandez, D. et al.: *Soft Matter* 16.13 (2020)

Initial conditions

- What are appropriate initial conditions?
- In experiments, cells settle at random locations within the initial spot and grow to small micro-colonies.
- In the model, we position initial "cell patches" at random locations in the domain centre $\Omega_0 = \{x \in \mathbb{R}^2 : \|x\| \leq R_0\} \subset \Omega$.
- Each model patch represents 1 microcolony $\Rightarrow$ tool to modulate founder density.
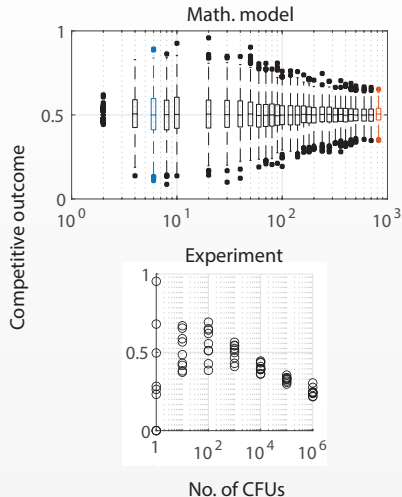

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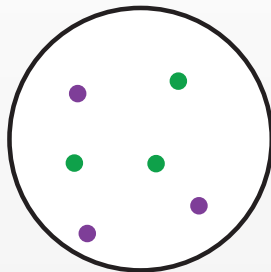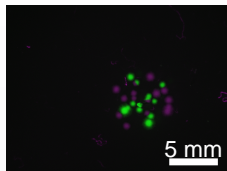
Variability in competitive outcome

- High founder density: no spatial structure and initial strain ratio consistently determines competitive outcome.

- Low founder density: spatial segregation occurs. Large variability in competitive outcome for fixed initial strain ratio.

- Founder density significantly affects phenotype and variability in competitive outcome.
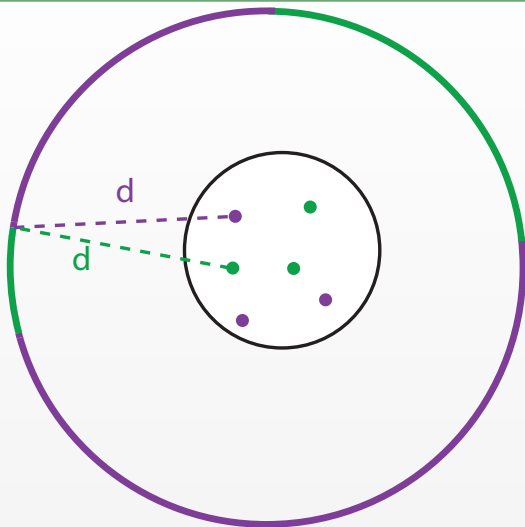
low founder density high founder density

Experiment Math. model Experiment Math. model
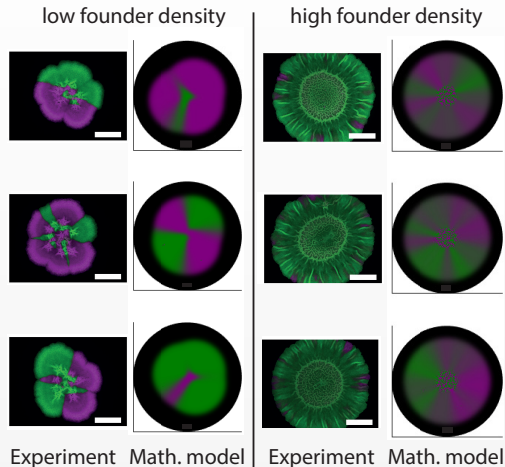
- **Founder density significantly affects phenotype and variability in competitive outcome.**
- Variability increases with decreasing founder density.
- Note the computational power of the mathematical model: 1000 model simulations each vs 12 technical replicates each of experimental assay.

Math. model

Experiment

Competitive outcome

No. of CFUs

- Hypothesis: only initial patches that can drive the biofilm's radial expansion contribute to outcome density.
- We define a quantity that, based on the initial cell locations, measures a strain's "access to free space"
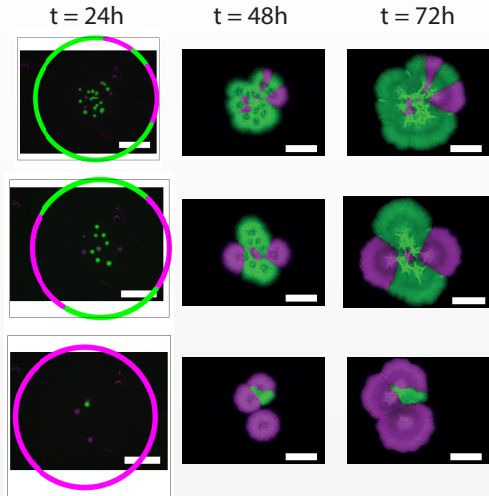
Disentangling variability

- Hypothesis: only initial patches that can drive the biofilm's radial expansion contribute to outcome density.
- We define a quantity that, based on the initial cell locations, measures a strain's "access to free space"

Access to free space predicts outcome

- Access to free space determines competitive outcome in the absence of any other competitive dynamics (isogenic strains).

low founder density

$R^2 = 0.96919$

Competitive outcome vs. Access to free space score, AFS_1
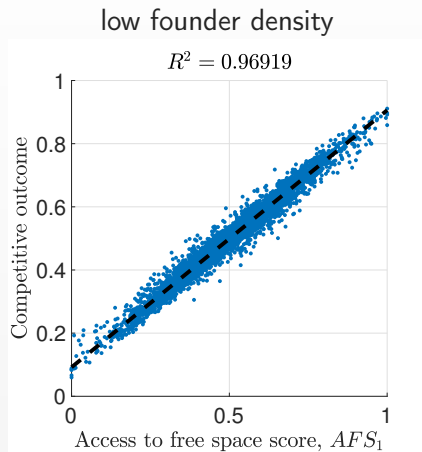
Access to free space predicts outcome

- Access to free space determines competitive outcome in the absence of any other competitive dynamics (isogenic strains).
- Slope of relation between access to free space and competitive outcome depends on founder density.

high founder density

$R^2 = 0.55095$

Competitive outcome vs. Access to free space score, AFS_1
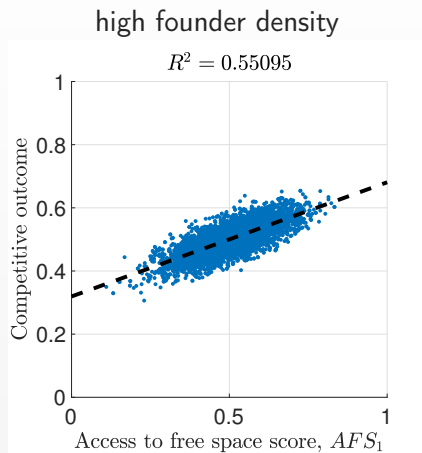
Non-isogenic strains

- Do these results also hold if strains are non-isogenic and interact through local antagonisms?

$$\frac{\partial B_1}{\partial t} = \nabla \cdot \left(\left(1 - \frac{B_1 + B_2}{k} \right) \nabla B_1 \right) \quad + B_1 \left(1 - \frac{B_1 + B_2}{k} \right) - B_1 B_2,$$

$$\frac{\partial B_2}{\partial t} = \nabla \cdot \left(d \left(1 - \frac{B_1 + B_2}{k} \right) \nabla B_2 \right) + r B_2 \left(1 - \frac{B_1 + B_2}{k} \right) - c B_2 B_1.$$

Nondimensional model, i.e. d, r, c are ratios of corresponding dimensional parameters.

Non-isogenic strains

- High founder density: competitive exclusion.

- Low founder density: spatial segregation enables coexistence.

- Decreases in founder density cause (i) increased variability in competitive outcome, (ii) higher (on average) densities of weaker strain.

low founder density

high founder density

Experiment   Math. model   Experiment   Math. model
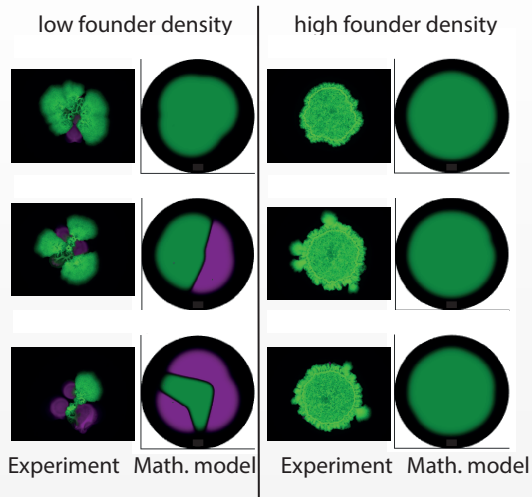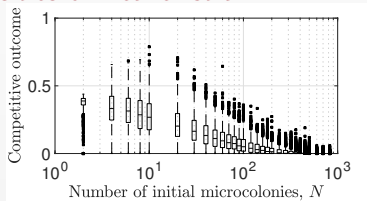
Access to free space predicts outcome

- Access to free space remains a reliable predictor of competitive outcome for low founder densities.
- Competition for space is the dominant mode of interaction for low founder densities.
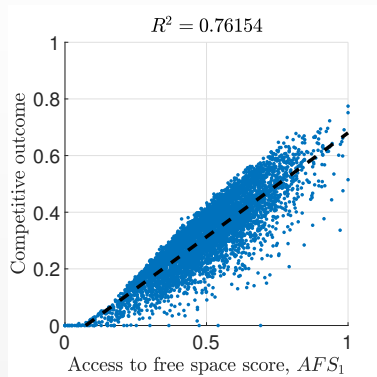
$$R^2 = 0.76154$$

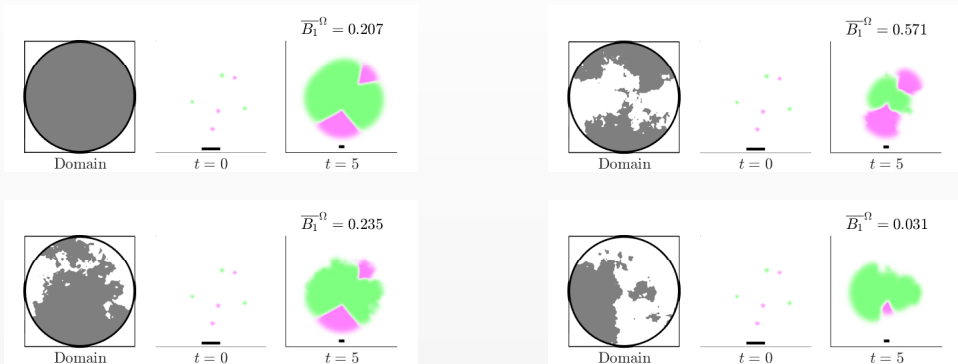Competitive outcome vs. Access to free space score, AFS_1

Impact of spatial heterogeneity

Q: What if environmental conditions are spatially heterogeneous?

$$\frac{\partial B_1}{\partial t} = \nabla \cdot \left(d_1(\mathsf{x}) \left(1 - \frac{B_1 + B_2}{k} \right) \nabla B_1 \right) + r_1(\mathsf{x}) B_1 \left(1 - \frac{B_1 + B_2}{k} \right) - c_{12} B_1 B_2,$$

$$\frac{\partial B_2}{\partial t} = \nabla \cdot \left(d_2(\mathsf{x}) \left(1 - \frac{B_1 + B_2}{k} \right) \nabla B_2 \right) + r_2(\mathsf{x}) B_2 \left(1 - \frac{B_1 + B_2}{k} \right) - c_{21} B_1 B_2.$$

Impact of spatial heterogeneity

Q: What if environmental conditions are spatially heterogeneous?

A: Spatial heterogeneity adds more variability $\Rightarrow$ Access to free space score cannot make accurate predictions.

Q: Which source of variability (low founder density or spatial heterogeneous environmental conditions) dominates?

Impact of spatial heterogeneity

Q: Which source of variability (low founder density or spatial heterogeneous environmental conditions) dominates?
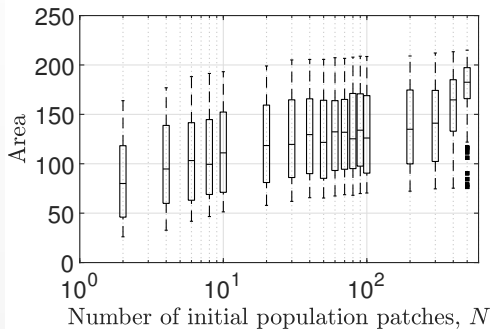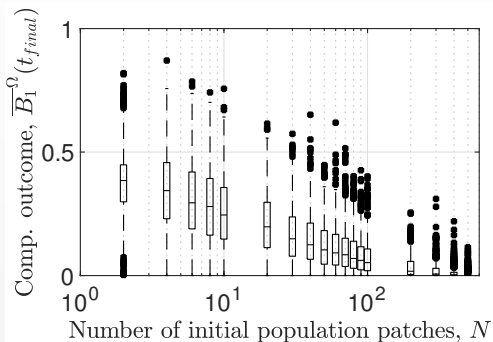
A: Low founder density determines variability in competitive outcome but spatial heterogeneities determine variability in footprint.
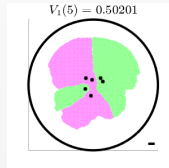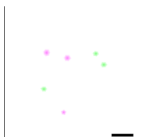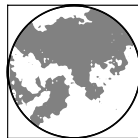
Q: Can we still make predictions of competitive outcome?

Predictions of competitive outcome in heterogeneous landscapes

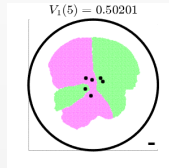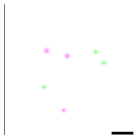Q: Can we still make predictions of competitive outcome?
A: Yes, using Voronoi tessellations based on an appropriate metric.

$V_1(5) = 0.50201$
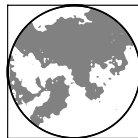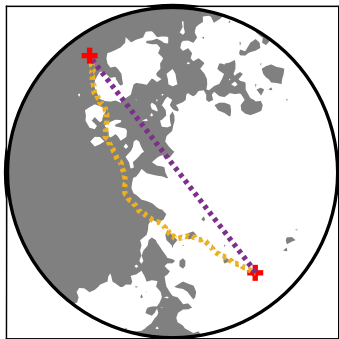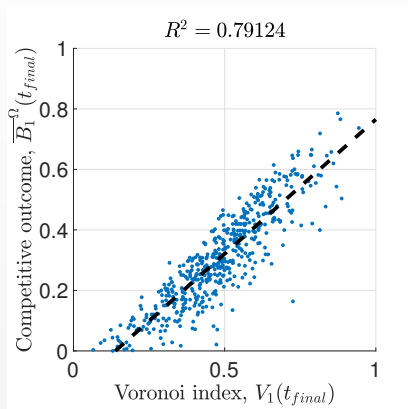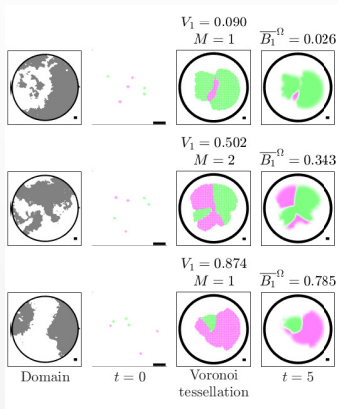
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Predictions of competitive outcome in heterogeneous landscapes

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A: Yes, using Voronoi tessellations based on an appropriate metric.

Conclusions

- Large variability in competitive outcome occurs for biofilms inoculated at low founder density, induced by the random positions of founder cells within the inoculum.
- Large variability in biofilm footprint occurs in spatially heterogeneous environments.
- Competitive outcome can be predicted based on founder cell locations and information on the spatial environment.
- Predictions hold true even if kin discrimination occurs $\Rightarrow$ "Race for space" is more important than antagonistic actions at low founder densities.
- Impact on applications (e.g. use of *B. subtilis* as biofertilizer): Competitive success across all founder densities can only be guaranteed if a strain spreads fast and kills efficiently.

Acknowledgements

Collaborators:

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- Graeme Ball (Univ. of Dundee)
- Cait E. MacPhee (Univ. of Edinburgh)
- Nicola R. Stanley-Wall (Univ. of Dundee)
- Fordyce A. Davidson (Univ. of Dundee)

References

Slides are available on my website.
`http://lukaseigentler.github.io`

[1] Eigentler, L., Davidson, F. A. and Stanley-Wall, N. R.: 'Mechanisms driving spatial distribution of residents in colony biofilms: an interdisciplinary perspective'. *Open Biol.* 12.220294 (2022).

[2] Eigentler, L., Kalamara, M., Ball, G., MacPhee, C. E., Stanley-Wall, N. R. and Davidson, F. A.: 'Founder cell configuration drives competitive outcome within colony biofilms'. *ISME J* 16.6 (2022), pp. 1512–1522.

[3] Eigentler, L., Stanley-Wall, N. R. and Davidson, F. A.: 'A theoretical framework for multi-species range expansion in spatially heterogeneous landscapes'. *Oikos* 2022.8 (2022), e09077.

Additional slides

Q: Can we still make predictions for competitive outcome?

Predictions of competitive outcome in heterogeneous landscapes

Q: Can we still make predictions for competitive outcome?

A: Yes, using Voronoi tessellations based on an appropriate metric.

Let $\mathcal{P}(x, y) := \{P = p([0, 1]) \subset \Omega, \text{where } p : [0, 1] \to \Omega : p \in \mathcal{C}^1 \text{a.e.}, p(0) = x, p(1) = y\}$ be the set of all paths from x to y. For a given path $P \in \mathcal{P}(x, y)$, the time taken to move along the path is given by

$$I(P) := \int_P \frac{1}{c(x)} ds = \int_0^1 \frac{1}{c(p(\tau))} \|p'(\tau)\| d\tau,$$
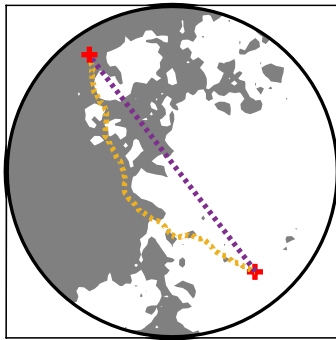
where $0 \leq c(x) < \infty$ represents the propagation speed along the path P. We define the *front propagation metric* from x to y as

$$t_{\text{FP}}(x, y) := \inf_{P \in \mathcal{P}(x, y)} I(P).$$

Q: Can we still make predictions of competitive outcome?
A: Yes, using Voronoi tessellations based on an appropriate metric.

Predictions of competitive outcome in heterogeneous landscapes

Q: Can we still make predictions for competitive outcome?
A: Yes, using Voronoi tessellations based on an appropriate metric.
Voronoi tessellation of whole domain:

$$\Delta_{B_i}^{\Omega} := \left\{ x \in \Omega : \min_{x_i \in \mathcal{B}_i} t_{\mathsf{FP}}(x, x_i) \leq \min_{x_j \in \mathcal{B}_j} t_{\mathsf{FP}}(x, x_j), i \neq j \right\},$$

where $\mathcal{B}_i := \{ x \in \{x_1, \dots x_N\} : B_i(x, 0) > 0 \}, i = 1, 2.$
Restrict to area expected to be occupied by time t:

$$\Delta_{B_i}(t) := \left\{ x \in \Delta_{B_i}^{\Omega} : \min_{y \in \mathcal{B}_i} t_{\mathsf{FP}}(x, y) \leq t \right\}, \quad i = 1, 2.$$

Voronoi index:
$$V_i(t) := \frac{\mathsf{Area}\left(\Delta_{B_i}(t)\right)}{\mathsf{Area}\left(\Delta_{B_1}(t)\right) + \mathsf{Area}\left(\Delta_{B_2}(t)\right)}, \quad i = 1, 2,$$

$V_i(5) = 0.50201$