

Simulating Organogenesis in COMSOL Multiphysics®

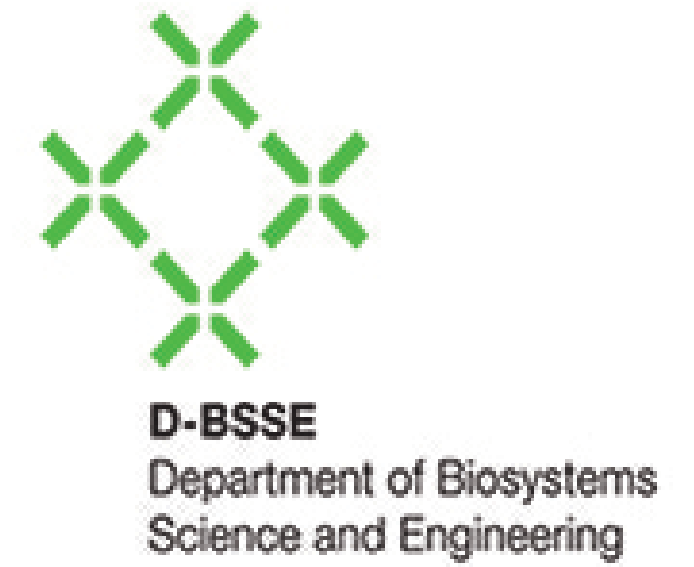
Image-based Modeling

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Limb bud Development

Organogenesis is a highly dynamic process that is tightly regulated during embryogenesis. We use image-based geometries with several subdomains for simulations of organogenesis on growing domains in COMSOL Multiphysics® using the Livelink™ for Matlab®.

Image-based Modeling of Organogenesis on Growing Domains

Our models are defined as a set of n reaction-diffusion equations in the form of:

$$\underbrace{\dot{C}_i}_{\text{reaction}} + \underbrace{u \nabla C_i}_{\text{advection}} + \underbrace{C_i \nabla u}_{\text{dilution}} = \underbrace{D_i \Delta C_i}_{\text{diffusion}} + \underbrace{R_i(C_1, \dots, C_n)}_{\text{reaction}}$$

where C_i represents the concentration of component i , D_i denotes the diffusion coefficient and u refers to the velocity of domains.

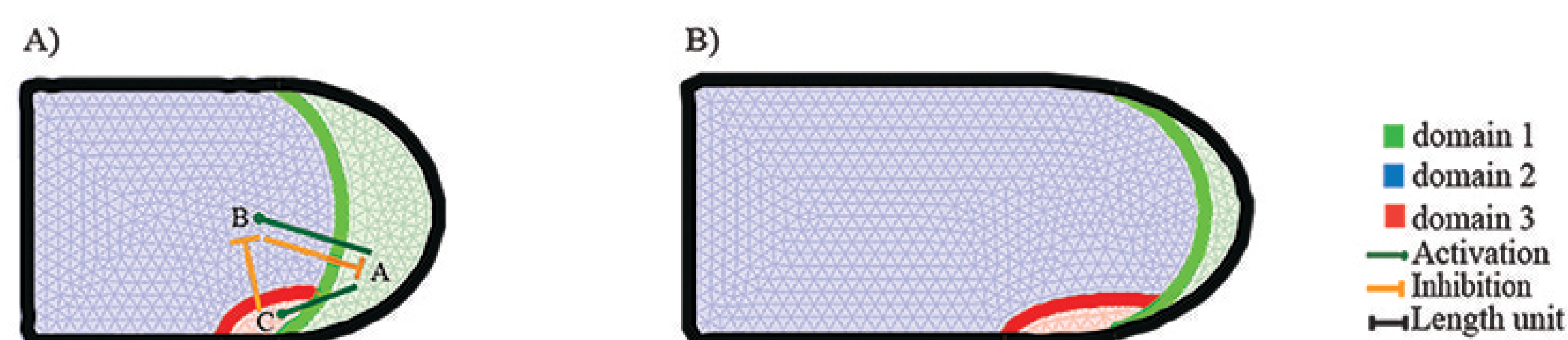


Figure 1. An idealized 2D limb bud domain at two different time points. The entire domain is divided into three subdomains (domain1 – green, domain2 – blue, domain3 – red). The domains and subdomains deform during development. (A) Domain at time t , and (B) at $t+1$. The network in panel A consists of three components, A, B and C. These components are produced and regulated in specific subdomains: A is produced and is inhibited only in domain1, C is activated only in domain3, and B is activated and repressed in the entire domain. All components diffuse in all domains.

Growing Domains and subdomains

To describe the growing domains, we need to calculate the displacement fields between the two shapes at t and $t+1$. We uniformly map these curves such that the Euclidean distance between each two points is equal on a curve (Figure 2).

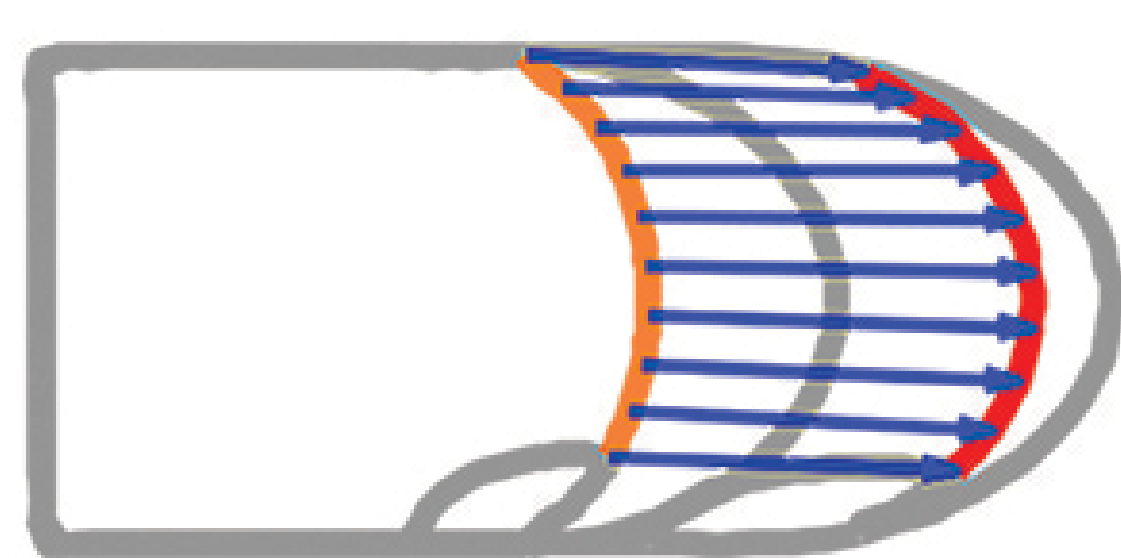


Figure 2. Displacement fields. Blue arrows show the displacement fields between two curves at two time steps, t (orange) and $t+1$ (red).

The introduction of subdomains results in intersecting boundary curves. To displace the intersection points, boundary curves are split at the intersection point such that boundary curves no longer contain intersections.

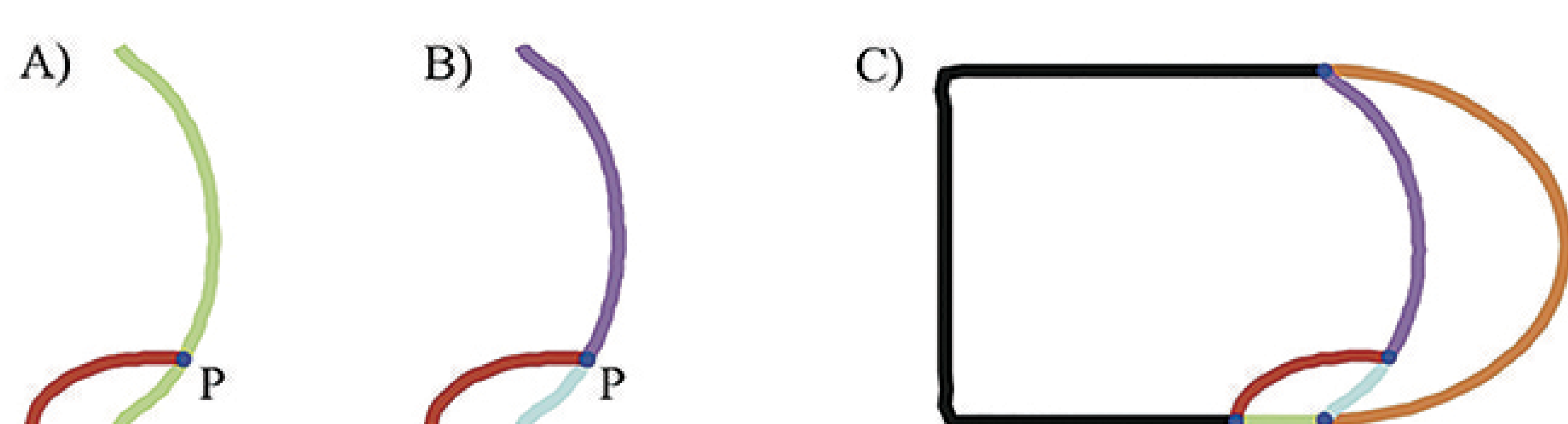


Figure 3. Framework to deal with intersecting boundary curves. (A) Curve1 (green) and curve2 (red) of Figure 1 intersect at point P . (B) To map the intersection point (blue point) at time t to the intersection point at $t+1$, the curves are divided into segments, such that the point P becomes the start/end point of the intersecting curves. (C) This algorithm is applied to all curves of Figure 1A. Curve1 is divided into two segments; Curve3 is divided into three segments, whereas Curve2 has only one segment. Model 1 is the model before segmentation and Model2 is the model after employing this framework.

Importance of Correct Intersection Point Mapping

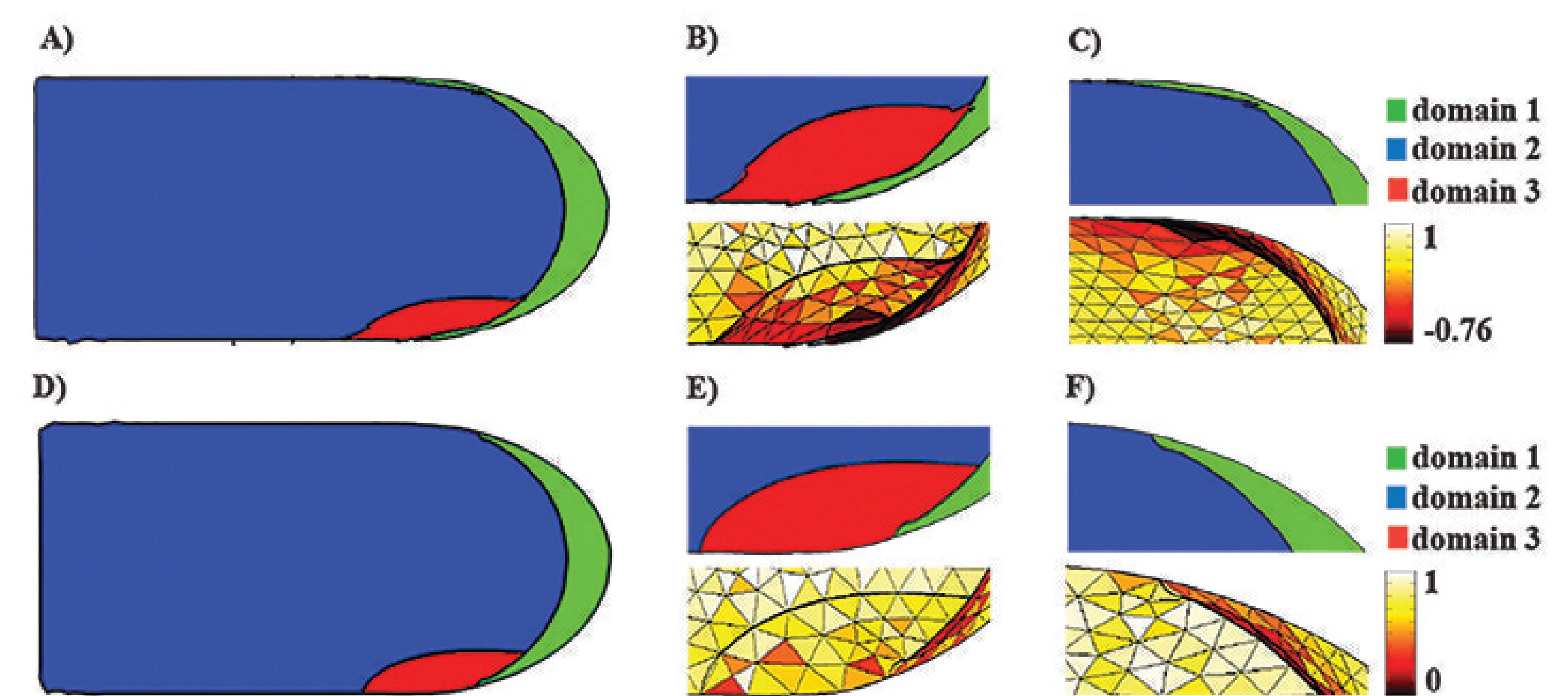


Figure 4. The deformed domain at the final time point. (A-C) Final deformed domain at time $t+1$ with intersecting boundary curves. In this case, not only the intersection points are not displaced correctly, but also their adjacent points are displaced improperly. (B,C-bottom) Inaccuracies in the mapping of the intersection points result in inverted meshes close to these points. (D-F) Final deformed domain at time $t+1$ using non-intersecting boundary curves. The intersection points and their neighbors are displaced perfectly. (E,F-bottom) High quality meshes close to the intersection points. The color bar indicates the quality of mesh elements; negative values indicate inverted meshes.

The inverted meshes that result from inaccuracies in the mappings lead to differences in the domain areas (Figure 5) and expression patterns of components (Figure 6).

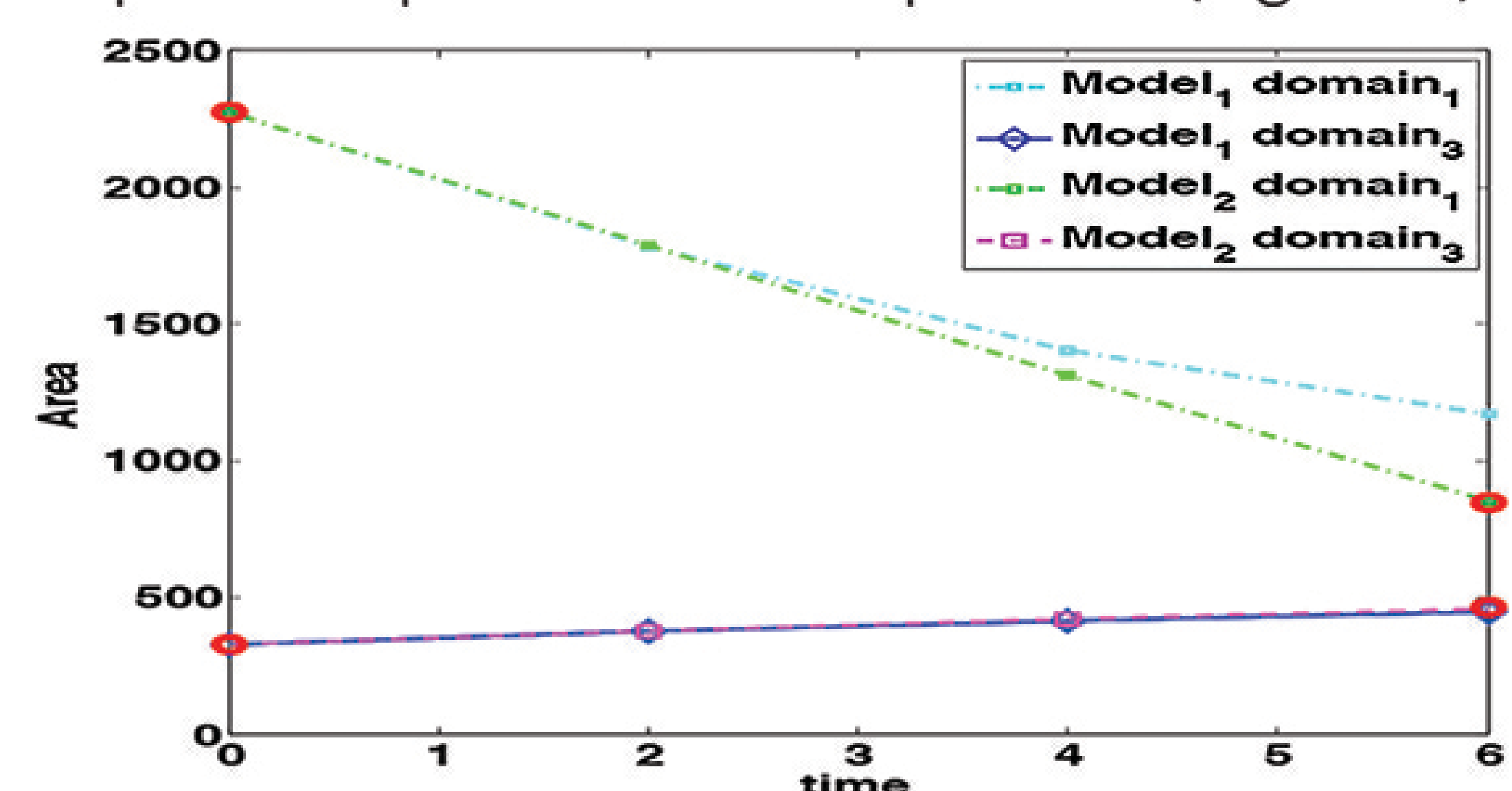


Figure 5. The domain areas over simulation time in case of intersecting (Model 1) or non-intersecting (Model 2) boundary curves. The real areas (red circles) of the domains at time t and $t+1$ are provided for comparison.

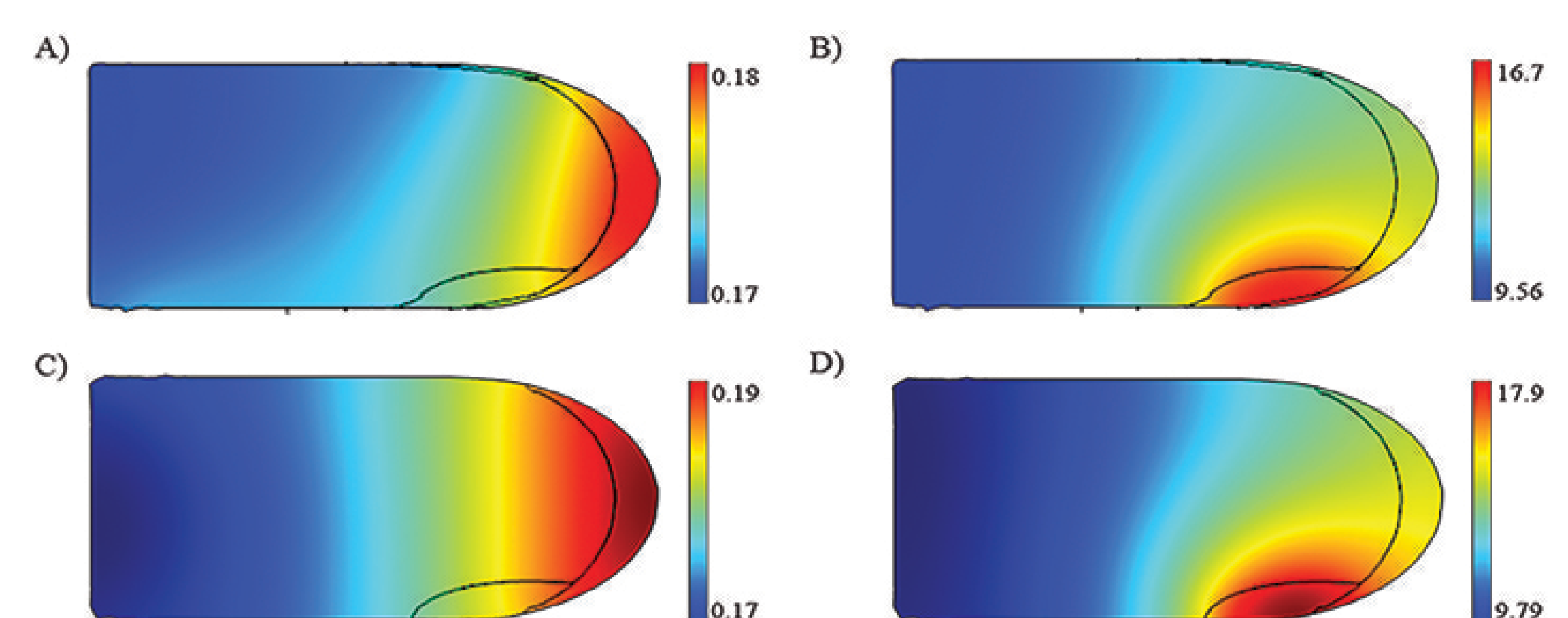


Figure 6. Expression patterns. Effective production rate as predicted in case of intersecting boundary curves for (panel A) species A, and (panel B) species C, and predicted in case of non-intersecting boundary curves for (panel C) species A, and (panel D) species C.

Conclusion

Using the standard COMSOL Multiphysics® Interpolation function, intersecting boundaries are not mapped correctly. We introduced a segmenting boundaries framework to solve this problem. This approach permits the simulation of large, complex regulatory networks on physiological growing domains.

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