Cancer phylodynamics

https://doi.org/10.1038/s41559-023-01996-z

Modelling evolution at the boundaries of solid tumours

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A mathematical model of eco-evolutionary dynamics estimates different birth rates of cells at the periphery of a tumour versus its centre, giving insight into locally stable evolutionary mechanisms that arise as a result of boundary-driven growth.

Functional modelling of the ecosystem of a tumour has long been an important goal of mathematical oncology. A great deal of effort has been exerted to derive cancer models that contain all of the elements that are necessary and sufficient to model cancer growth, but these theoretical efforts have diverged widely over the past half century. Meanwhile, empiricists have added layers of complexity in phylogenetic models to obtain as close to a realistic experimental representation of a tumour as possible. However convenient it may appear to be to study cancer cells in isolation, this has many of the same drawbacks as attempting to understand animals by studying them in a zoo. Even the simplest of eco-evolutionary theories add a great deal of complexity to an already dynamic system; in particular, spatially conserved clonal selection as an emergent feature of microenvironment-mediated growth is of special interest to this community.

Writing in *Nature Ecology & Evolution*, Lewinsohn and colleagues build a Bayesian state-dependent evolutionary phylodynamic model (known as SDevo) that tries to mimic several aspects of the "evolutionary and ecological process wherein cellular subpopulations expand and diversify" in a tumour[1]. But, as opposed to classical natural selection models, the authors present a boundary model in which proximity to the tumour boundary affects fitness, thus modifying the growth patterns as compared to pure selection (Fig. 1).

The authors show how SDevo can use spatial and temporal aspects of collected data to infer varying expansion rates given initial conditions and sampling strategies. Agent-based models are standard tools for investigating microevolutionary dynamics, and the authors compare differential birth rates in such a model on a 2D lattice under boundary-restricted and unrestricted conditions. In these simulations, the authors establish that the mutation aggregation rate is positively correlated with time spent at the tumour periphery. This effect weakens with increasing cellular turnover rate, which effectively takes the evolutionary pressure off. SDevo is then developed to infer birth rates as a function of adjacency to the tumour centre in simulated tumour growth, incorporating total mutation aggregation per lineage per simulation time as an evolutionary parameter. SDevo is further shown to outperform preestablished tools in small sample groups, but requires stricter constraints with an increase in the time spent by lineages on tumour edges.

Next, the authors test SDevo under simulated varying sampling conditions, such as maximal distance and random sampling. As SDevo performs reasonably well in most of these agent-based-model-derived samples, the authors then test it with off-lattice physics-driven simulations in which neighbourhood mechanical pressure is a proxy for boundary conditions. To mimic clinical samples taken from tumour cross-sections, the tool is then used to analyse *z*-axis-wide 'slices' taken from 3D tumour simulations. The boundary-driven growth estimates run into some problems in these complex situations, but the extent to which SDevo could estimate boundary-driven growth dynamics in both spatially determined and cell-fitness-mediated tumour growth is still encouraging. Finally, SDevo is tested on two microbiopsied

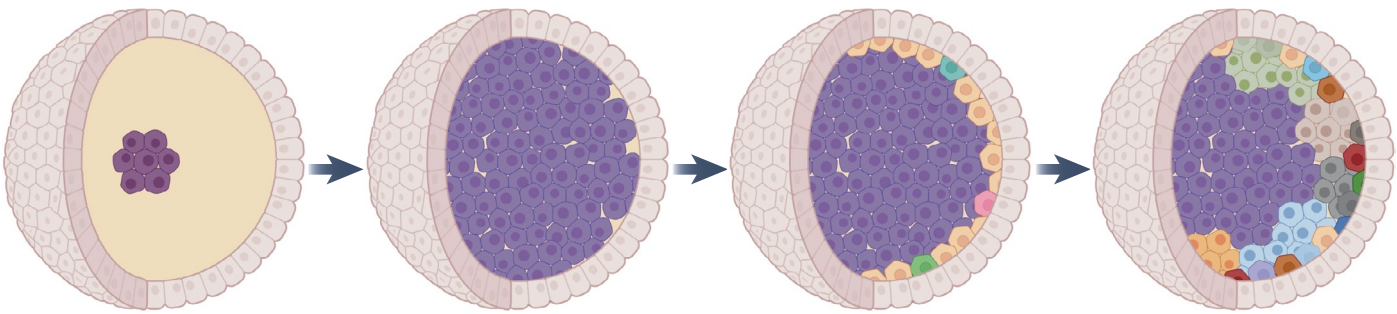

Fig. 1 | Boundary-driven phylodynamics in solid tumours. A tumour begins as a small cluster of typically homogeneous cells that share a common ancestor (depicted in purple). Without constraints on space and resources during expansion, cellular phylogenies may remain stable. As the tumour reaches the carrying capacity set by its environment, the cells on the periphery experience higher proliferation rates over time as compared to the tumour core. If cell turnover rate remains globally unchanged, this results in more phylogenetically distant peripheral progenies the more time they spend in the boundary (shown in diversifying colours around the tumour periphery). By contrast, from outside looking in, the tumour core will appear to remain evolutionarily stable. Created with BioRender.com.

liver tumours in which samples are geotagged in 3D space, providing their location relative to the tumour core. Here, the algorithm detects some boundary-driven growth but also encounters familiar reasons for model breakdown: a lack of samples, nonuniform sampling and environment-specific heterogeneity (in this case, native branching patterns).

The framework provides evolutionary explanations for some hitherto inexplicable phenomena in cancer, such as why many driver mutations appear late and are subclonal[2] or why slow-growing tumour subpopulations do not naturally go extinct[3]. Fundamentally, boundary-driven growth is a reasonable assumption for tumour expansion only given rigid spatial constraints. Therefore, it might be impractical to generalize growth conditions even for an isolated single class of omnidirectionally growing tumours. The silver lining, as the authors note, lies in the capacity to extend SDevo to other growth models (for example, in a unidirectional invasion front along a hard surface or in glandular compartments). A strong assumption in these conditions is equivalence given equal Euclidean distance from the tumour core, which is rarely true because growth-determining factors (such as hypoxia or angiogenesis) are anything but homogeneous. Furthermore, the model discounts islands of necrotic tissue, a common feature of solid tumours that can represent local boundaries. Nevertheless, looking ahead from tumour growth, SDevo could develop to estimate boundary-driven conditions (for example, diffusion gradients) of clinically relevant tumour phenotypes.

Some of the authors of the Lewinsohn et al. article have previously studied the effects of migration patterns (for which boundary-driven growth is a proxy) in viral population genetics (HIV or SARS-CoV-2) and developed ways to estimate such patterns in Bayesian framework[4,5]. These analyses reflected how individuals under migration can experience selection pressures that are different from those of their physically stationary and phylogenetically conserved counterparts, and brought focus on atypical evolutionary changes that result in spatial heterogeneity and differential expansion patterns at the boundary of a spatially restricted population. With this current work, Lewinsohn et al. have demonstrated how the evolutionary philosophy of boundary-driven growth adds a necessary layer of complexity to the existing literature of tumour growth modelling.

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Published online: 9 March 2023

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Competing interests

The authors declare no competing interests.